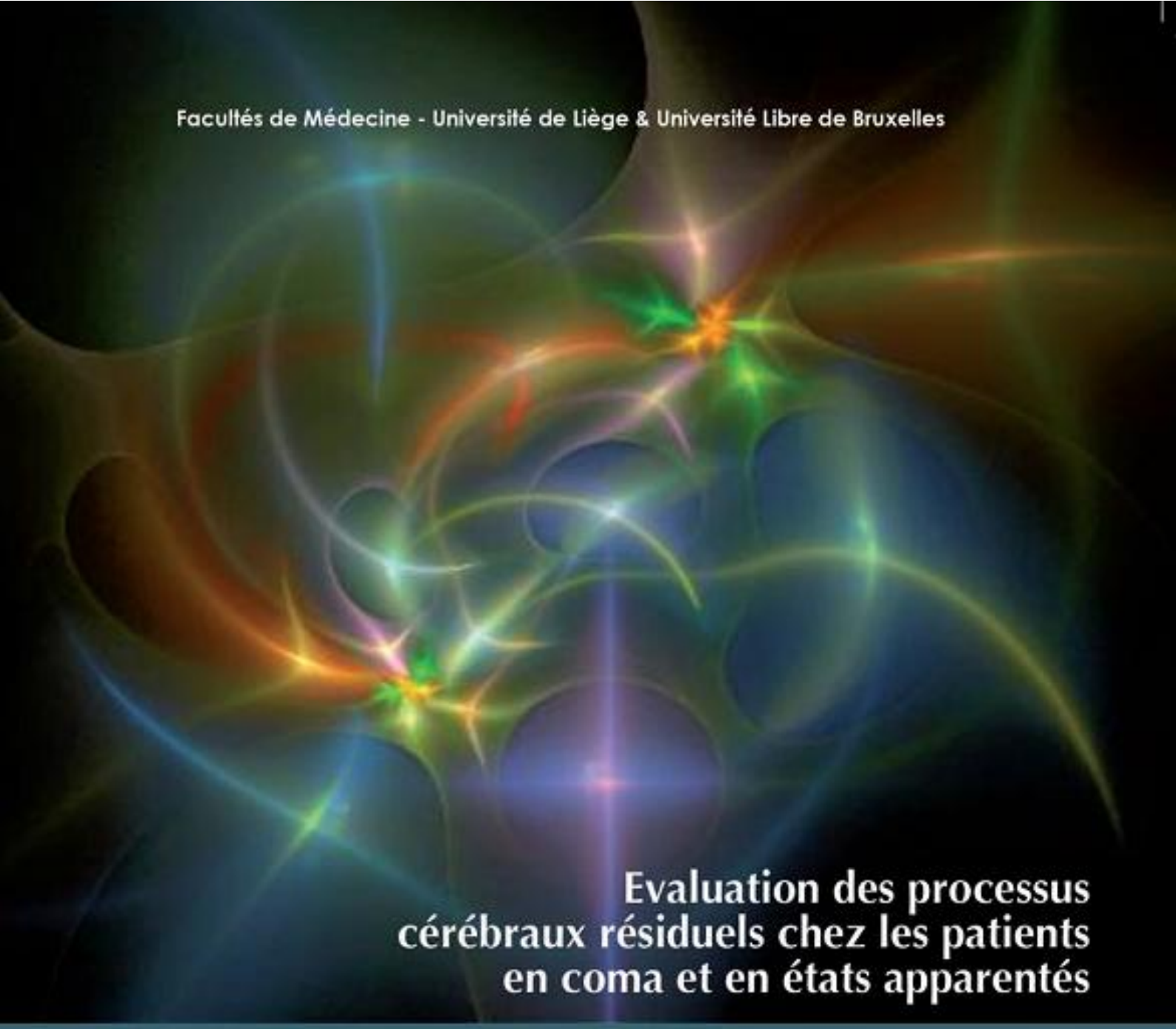
Facultés de Médecine - Université de Liège & Université Libre de Bruxelles



Evaluation des processus cérébraux résiduels chez les patients en coma et en états apparentés

Etude par électroencéphalographie et par stimulation magnétique transcrânienne

Thèse présentée par Olivia GOSSERIES en vue de l'obtention du grade de Docteur en Sciences Biomédicales et Pharmaceutiques

Sous la direction des Prs. Steven LAUREYS et Serge GOLDMAN

Coma Science Group, Centre de Recherches du Cyclotron
Laboratoire de Cartographie Fonctionnelle du Cerveau
Département de Neurologie, CHU Sart Tilman

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UNIVERSITE DE LIEGE & UNIVERSITE LIBRE DE BRUXELLES
Facultés de Médecine

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« Il faut toujours viser la lune, car même en cas d'échec, on atterrit dans les étoiles »
(Oscar Wilde)

A ma mimi,

A mes parents fantastiques,

A mon frère chéri & mes amis de toujours

Table des matières

Remerciements....3
Liste des publications....5
Abréviations....10
Résumé....11
Summary....13
CHAPITRE 1. INTRODUCTION GENERALE....15
1.1. Notion de conscience....16
1.2 Etats de conscience altérée....18
1.2.1 Mort cérébrale....19
1.2.2 Coma....20
1.2.3 Syndrome d'éveil non-répondant (état végétatif)....20
1.2.4 Etat de conscience minimale....21
1.2.5 Locked-in syndrome....22
1.3 Evaluation clinique....23
1.4 Evaluation par neuroimagerie....25
1.4.1 Mesures des lésions structurelles....25
1.4.2 Mesure de l'activité cérébrale au repos....25
1.4.3 Mesure de l'activité cérébrale en réponse à des stimulations sensorielles....28
1.4.4 Communiquer sans parole ni geste via des paradigmes actifs....30
1.5 Objectifs de ce travail....31
CHAPITRE 2. PREDIRE LA RECUPERATION INDIVIDUELLE....34
2.1 Introduction....35
2.2 Evaluation pronostique comportementale au stade subaigu....37
2.3 Conclusion....40
CHAPITRE 3. MESURES ELECTROENCEPHALOGRAPHIQUES COMME OUTIL DIAGNOSTIQUE ET PRONOSTIQUE....42
3.1 Introduction....43
3.2 EEG-entropie....47
3.3 Potentiels évoqués auditifs....52
3.4 Conclusion....58

CHAPITRE 4. STIMULATION MAGNETIQUE TRANSCRANIENNE COMME MESURE DES CONNEXIONS CORTICO-SPINALES.....60

4.1 Introduction 61

4.2 Excitabilité cortico-spinale anormale chez les patients en état de conscience altérée 63

4.3 Conclusion 68

CHAPITRE 5. STIMULATION MAGNETIQUE TRANSCRANIENNE COUPLEE A L'ELECTROENCEPHALOGRAPHIE COMME MESURE DES CONNEXIONS CORTICO-CORTICALES.....70

5.1 Introduction 71

5.2 Qu'en est-il des patients récupérant du coma?.....72

5.3 Dissociation entre les mécanismes de connectivité, les systèmes d'éveil et l'activité électrique spontanée.....76

5.4 Combinaison avec les données IRM et TEP 78

5.5 Conclusion 79

CHAPITRE 6. ASPECTS PSYCHOLOGIQUES LIES A LA PRISE EN CHARGE DES PATIENTS SEVEREMENT CEREBROLESES 83

6.1 Introduction 84

6.2 Burnout chez le personnel soignant.....84

6.3 Importance et satisfaction des besoins des familles.....88

6.4 Conclusion 91

CHAPITRE 7. CONCLUSIONS ET PERSPECTIVES FUTURES 93

Références.....101

Annexes: publications scientifiques et questionnaires.....121

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Abréviations

CRS-R	Echelle de récupération du coma (Coma Recovery Scale-Revised)
CT-scan	Scanographie (Computed Tomography)
DCM	Modélisation causale dynamique (Dynamic Causal Modeling)
DRS	Disability rating scale
EEG	Electroencéphalographie
EMCS	Sortie de l'état de conscience minimale (Emergence of the Minimally Conscious State)
IRMf	Imagerie par résonance magnétique fonctionnelle
LIS	Locked-in syndrome
MCS	Etat de conscience minimale (Minimally Conscious State)
MMN	Négativité de discordance (Mismatch Negativity)
NTBI	Lésion cérébrale d'étiologie non-traumatique (Non Traumatic Brain Injury)
PE	Potentiels évoqués
PEM	Potentiels évoqués moteurs
SPM	Statistical parametric mapping
SPSS	Statistical package for the social sciences
SMR	Seuil moteur au repos
SMT	Stimulation magnétique transcrânienne (Transcranial Magnetic Stimulation, TMS)
TBI	Lésion cérébrale d'étiologie traumatique (Traumatic Brain Injury)
TEP	Tomographie à émission de positons
UWS/VS	Syndrome d'éveil non répondant/état végétatif (Vegetative State/Unresponsive Wakefulness Syndrome)

Résumé

Après un coma, certains patients restent de manière prolongée dans un état d'éveil non-répondant (éveil sans conscience) ou en état de conscience minimale (éveil et fluctuation de la conscience) (Gosseries & Bruno *et al.*, 2011b). Des travaux antérieurs ont montré que l'évaluation comportementale aboutissait fréquemment à des erreurs diagnostiques. Des études de neuroimagerie en IRM et TEP se sont développées pour mesurer plus objectivement l'état de conscience de ces patients (Gosseries *et al.*, 2011d). Ces techniques ne sont cependant pas encore assez sensibles pour détecter des signes de conscience au niveau individuel. Le premier objectif de ce travail est de valider de nouveaux marqueurs diagnostiques paracliniques en utilisant d'autres outils tels que l'électroencéphalographie et la stimulation magnétique transcrânnienne. D'un point de vue neuroscientifique, les théories de l'information intégrée (Tononi, 2004), de l'espace de travail neuronal global (Dehaene et al, 2006) et du syndrome de déconnexion (Laureys *et al.*, 2005c) émettent l'hypothèse qu'un réseau neuronal largement connecté et spécialisé est requis pour l'émergence de la conscience. Ces modèles proposent un parallèle entre la connectivité au sein d'un large réseau fronto-pariéto-thalamique et le degré de conscience d'un sujet. Le second objectif de notre travail est de tester ces hypothèses, en intégrant nos résultats dans un cadre théorique général de la conscience.

Evaluation comportementale. Avant de plonger dans le vif du sujet, nous avons évalué des facteurs pronostiques à court terme de la récupération fonctionnelle après un coma. L'intervalle de temps entre la lésion cérébrale et l'admission dans un centre de réadaptation, le score à la Disability Rating Scale à l'admission et l'étiologie semblent de bons facteurs pronostiques. Nos modèles de prédiction ne peuvent cependant pas être utilisés dans le cadre des décisions cliniques individuelles, en raison d'une trop grande variabilité entre les patients (Gosseries & Whyte *et al.* 2009).

Evaluations électroencéphalographiques (EEG). Une mesure automatisée d'EEG-entropie a permis de discriminer entre les patients conscients et inconscients dans les stades aigus avec une très bonne sensibilité (Gosseries *et al.*, 2011b). Les valeurs de l'EEG-entropie étaient élevées chez les patients en état de conscience minimale alors qu'elles étaient basses chez les patients en état d'éveil non-répondant, suggérant une diminution de la complexité cérébrale chez ces derniers. Cette technique, qui est facilement applicable en routine clinique, n'a par contre montré aucune valeur pronostique. Une seconde mesure a ensuite été évaluée à l'aide des potentiels évoqués auditifs combinés à des analyses spécifiques de reconstruction de source. Ces données ont montré une altération des connexions cortico-corticales (connexions rétrogrades fronto-temporales) chez les patients en état d'éveil non-répondant (Boly *et al.*, 2011a). Ces résultats nécessitent encore une validation au niveau individuel mais soulignent l'importance des projections neuronales rétrogrades dans l'émergence de la conscience, et confirment les hypothèses de la perte de connectivité effective et du syndrome de déconnexion chez les patients en état de conscience altérée.

Stimulation magnétique transcrânienne (SMT). Nous avons ensuite utilisé la technique SMT pour mesurer les connexions cortico-spinales. Les mesures électromyographiques ont montré des résultats globalement similaires au niveau périphérique alors que les mesures corticales différaient selon le niveau de conscience. En effet, le seuil moteur, les courbes de recrutement et l'inhibition afférente à courte latence étaient altérés chez les patients, et les deux dernières mesures étaient en lien avec le niveau de conscience des patients (Gosseries &

Lapitskaya *et al.*, soumis). Ces résultats suggèrent donc une diminution de l'excitabilité et de l'inhibition cortico-spinale, ainsi qu'un syndrome de déconnexion d'origine corticale chez les patients en état de conscience altérée.

Combinaison de la SMT et de l'EEG. Enfin, nous avons évalué directement l'effet de la SMT sur l'activité du cortex cérébral (Gosseries & Rosanova *et al.*, soumis). Cette méthode a permis de différencier au niveau individuel les patients en état d'éveil non-répondant des patients en état de conscience minimale. Chez les premiers, la réponse était initialement plus forte mais s'éteignait rapidement et ne se dispersait pas au-delà du site de stimulation. Chez les patients en état de conscience minimale, une réponse initiale au site de stimulation était suivie par une séquence complexe d'ondes qui se propageaient aux aires corticales adjacentes. Les patients présentant une récupération progressive de la conscience ont quant à eux montré une résurgence d'interactions cérébrales rapides et à longue distance (Gosseries & Rosanova *et al.*, 2012). La SMT-EEG semble être une technique sensible qui pourrait être utilisée comme marqueur diagnostique en routine clinique. Ces résultats confirment également un syndrome de déconnexion au niveau cortico-cortical et une perte de conscience liée à une altération de la connectivité effective entre les différentes aires cérébrales (perte d'intégration et de différentiation de l'activité neuronale).

Aspects psychologiques liés à la prise en charge des patients sévèrement cérébrolésés. Parallèlement aux études susmentionnées, nous avons évalué le syndrome du burnout parmi le personnel soignant prenant en charge des patients non communicants dans des centres de réadaptation et des maisons de repos. Sur 523 personnes interrogées, 18% présentaient un burnout modéré (15%) à sévère (3%). La profession (équipe infirmière), le lieu de travail (maison de repos) et le nombre d'heures passées avec les patients étaient associés à la présence de burnout (Gosseries *et al.*, accepté). L'importance et la satisfaction de différents besoins des familles des patients ont également été évaluées. Les besoins considérés comme importants étaient le besoin d'information médicale, le soutien émotionnel et social ainsi que l'implication dans les soins. Les familles étaient insatisfaites pour les trois premiers besoins rapportés et présentaient souvent des pensées dépressives et de l'anxiété (Gosseries *et al.*, soumis). Le burnout du personnel soignant et les besoins des familles doivent être pris en compte afin de réduire la détresse psychologique associée à la difficulté de la prise en charge de ces patients et afin de favoriser une qualité optimale des soins prodigués aux patients.

Au terme de ce travail, nous proposons des perspectives de futures études sous forme de deux nouvelles approches. La première approche, multimodale et longitudinale, consiste à comparer les différents types de connectivité cérébrale (structurelle, fonctionnelle, effective) lors de la récupération de conscience. La seconde approche est d'ordre thérapeutique, et vise à établir dans quelle mesure la restauration de la connectivité effective est liée à la restauration de conscience lors de traitements pharmacologiques et de stimulation cérébrale.

Summary

Following a coma, some patients may stay in a chronic unresponsive wakefulness syndrome (wakefulness without awareness) or in a minimally conscious state (wakefulness and fluctuation of awareness) (Gosseries & Bruno *et al.*, 2011b). Previous works showed that behavioral assessments frequently lead to diagnostic errors. Neuroimaging studies using MRI and PET were developed to measure more objectively the state of consciousness of these patients (Gosseries *et al.*, 2011d). However these techniques are not sensitive enough to detect signs of consciousness at the individual level. Our first objective is to validate new diagnostic paraclinical markers using electroencephalography and transcranial magnetic stimulation. At the neuroscientific level, the information integration (Tononi, 2004), the global neuronal workspace (Dehaene *et al.*, 2006) and the disconnection syndrome (Laureys and al, on 2005) theories postulate that activation of a widely connected and specialized neuronal network is required for consciousness to emerge. The level of consciousness can therefore be linked to the level of connectivity in a wide fronto-parieto-thalamic network. Our second objective is to test these hypotheses by integrating our results into a general theoretical frame of consciousness.

Clinical assessment. Outside the scope of our main objectives, we studied predictors of short-term outcome. The time interval post-injury and the Disability Rating Scale score at enrollment in a rehabilitation centre were predictors of early recovery. Etiology was also a good predictor in some analysis. None of these predictive models could however explain sufficient variance to allow their use in individual clinical decision making (Gosseries & Whyte *et al.*, 2009).

EEG assessment. We investigated the usefulness of EEG in differentiating unconscious from minimally conscious patients. Automated EEG-entropy could reliably discriminate these patients in the acute setting with a good sensitivity (Gosseries *et al.*, 2011b). EEG-entropy values were high in minimally conscious patients and low in unconscious patients, suggesting a decrease of neural network complexity in the latter. This technique, which is easily applicable in clinical routine, offered however no reliable prognosis information. In a second study, using auditory evoked potentials and specific source reconstruction analysis, we showed that the only difference between unresponsive patients and healthy controls was an impairment of backward connectivity from frontal to temporal cortices. By contrast, minimally conscious patients exhibited near-normal recurrent effective connectivity (Boly *et al.*, 2011a). These results require further validation at the individual level but emphasize the importance of top-down projections in recurrent processing for conscious perception, and confirm the hypotheses of the loss of effective connectivity and disconnection syndrome.

Transcranial magnetic stimulation assessment (TMS). We assessed cortico-spinal excitability through the stimulation of motor cortices and electromyography recordings. Spinal measurements were globally similar whereas cortical measurements differed according to the level of consciousness. Patients revealed a higher motor threshold, narrower stimulus/response curves and a decreased short afferent inhibition (using an additional electrical stimulation on the median nerve) compared to healthy controls participants. Recruitment curves and short afferent inhibition were associated to the level of consciousness. Our findings suggest decreased cortico-spinal excitability and inhibition as well as a cortical disconnection syndrome in disorders of consciousness (Gosseries & Lapitskaya *et al.*, submitted).

Multimodal TMS and EEG assessment. To further assess cortical excitability and effective cortico-cortical connectivity, we employed TMS combined with EEG (Gosseries & Rosanova *et al.*, submitted). This technique allowed to reliably discriminate between unresponsive and minimally conscious patients at the individual level. In unresponsive patients, TMS triggered a stereotyped and local response whereas in minimally conscious patients, TMS triggered rapidly changing and long-lasting widespread responses. Through longitudinal measurements, we also showed that this clear-cut change in the brain's capacity for internal communication occurred at an early stage during recovery of consciousness, before reliable communication could be established with the patient (Gosseries & Rosanova et al, 2012). TMS-EEG seems therefore a trustworthy tool which could be used as a diagnostic marker in clinical routine. These results also confirm the cortico-cortical disconnection syndrome and the loss of consciousness related to altered effective connectivity between brain areas (loss of integration and differentiation of the neuronal activity).

Psychological issues related to the management of patients with disorders of consciousness. In parallel to the above studies, we also investigated the presence of burnout among healthcare professionals working with unresponsive and minimally conscious patients in rehabilitation centres and nursing homes. Out of 523 caregivers, 18% presented a moderate (15%) to severe burnout (3%). Profession (*i.e.* nurse/nursing assistants), working place (*i.e.* nursing home) and the amount of time spent with patients were associated with burnout (Gosseries *et al.*, accepted). We also evaluated the family needs of chronic patients with disorders of consciousness. The most important needs reported were the medical information, the social and emotional support as well as the involvement in the care. Unsatisfaction was nevertheless observed for the emotional and social support as well as for medical information, in addition to frequent depressive thoughts and anxiety (Gosseries *et al.*, submitted). Insufficient consideration of professional workers burnout and family needs may lead to important psychological distress and may favor inadequate quality of care in patients with disorders of consciousness.

At the end of this work, we propose two new approaches in future studies. The first approach, multimodal and longitudinal, consists in comparing various types of connectivity (*i.e.* structural, functional and effective) during recovery of consciousness. The second approach is of therapeutic interest, and will allow to evaluate in which measure the restoration of effective connectivity is connected to the restoration of consciousness during pharmacological treatments and during brain stimulation.

CHAPITRE 1. INTRODUCTION GENERALE

"What is mind? No matter. What is matter? Never mind" (George Berkeley)

Sur base des articles suivants :

Gosseries O* & Bruno MA* (*co-premières), Chatelle C, Vanhaudenhuyse A, Schnakers C, Soddu A, Laureys S. Disorders of consciousness: What's in a name? *NeuroRehabilitation*, 28: 3-14, 2011.

Gosseries O* & Bruno MA* (*co-premières), Ledoux D, Hustinx R, Laureys S. Assessment of consciousness with electrophysiological and neurological imaging techniques. *Current Opinion in Critical Care*, 17(2): 146-5, 2011.

Gosseries O, Vanhaudenhuyse A, Bruno MA, Demertzi A, Schnakers C, Boly M, Maudoux A, Moonen G, Laureys S. Disorders of consciousness: coma, vegetative and minimally conscious states. *States of consciousness: experimental insights into meditation, waking, sleep and dreams*. D Cvetkovic & I Cosic, Springer-Verlag, Berlin, 29-55, 2011.

Gosseries O, Laureys S, Vanhaudenhuyse A. Comment évaluer la conscience chez des patients sévèrement cérébrolésés? *L'évaluation du traumatisme crânien*, Collection médico-légale, I Lutte, Anthemis, Limal, 12: 13-51, 2011.

Gosseries O, Demertzi A, Noirhomme Q, Tshibanda L, Boly M, de Beeck M, Hustink R, Maquet P, Salmon E, Moonen G, Luxen A, Laureys S, De Tiège X. Functional neuroimaging (fMRI, PET and MEG): what do we measure? *Revue Médicale de Liège*, 63(5-6): 231-7, 2008.

Grâce aux techniques de réanimation toujours plus performantes, de plus en plus de personnes survivent à de graves lésions cérébrales et certaines se retrouvent temporairement ou définitivement en syndrome d'éveil non-répondant (anciennement appelé état végétatif), en état de conscience minimale ou en locked-in syndrome. L'évaluation comportementale est actuellement l'outil principal pour établir un tel diagnostic mais la pratique clinique démontre qu'il reste encore difficile de détecter des signes de conscience au chevet des patients. Il est donc primordial de développer une expertise dans ce domaine et de répondre à la nécessité d'inclure des outils objectifs paracliniques afin d'affiner le diagnostic et d'optimaliser la prise en charge de ces patients. Parallèlement, l'étude des patients en état de conscience altérée constitue une approche lésionnelle dans la recherche des corrélats neuronaux de la conscience humaine. Nous allons dans cette introduction définir le terme 'conscience' et décrire brièvement les théories neuroscientifiques actuelles. Les différents états de conscience altérée rencontrés après un coma seront ensuite développés et nous aborderons les points essentiels de l'évaluation clinique de la conscience au chevet des patients. Enfin, nous passerons en revue les différentes études de neuroimagerie qui ont été réalisées jusqu'à présent chez ces patients et nous conclurons ce chapitre avec les objectifs de ce travail.

1.1. Notion de conscience

La conscience est un concept ambigu difficilement définissable (Zeman, 2001). Une définition, parmi tant d'autres, est que la conscience correspond à ce que nous perdons lorsque nous nous endormons profondément et ce que nous récupérons lorsque nous nous réveillons. Toutefois, lorsqu'elle est évaluée au chevet des patients, on s'accorde à dire que la conscience (*consciousness*) possède deux composantes : l'éveil (*wakefulness*) et la perception consciente (*awareness*). L'éveil se marque cliniquement par une ouverture prolongée des yeux et est sous-tendu par le tronc cérébral et ses projections thalamiques et corticales (Steriade, 1996; Vogt et Laureys, 2005). La perception consciente correspond à l'ensemble des expériences subjectives présentes et passées. Elle est définie au niveau clinique par des comportements volontaires tels qu'une réponse à la commande, et dépend du réseau fronto-pariétal et de ses connexions cortico-thalamiques. La conscience résulte donc de l'interaction entre l'activité du cortex cérébral, du tronc cérébral et du thalamus. L'éveil et la perception consciente sont généralement corrélés. Lors d'un sommeil profond, d'un coma ou d'une anesthésie générale, nous ne sommes ni éveillés ni conscients alors que lorsque nous sommes conscients, nous sommes éveillés. Une dissociation entre l'éveil et la perception consciente

existe cependant lors du sommeil paradoxal (conscience>éveil) et dans les états pathologiques tels que le syndrome d'éveil non-répondant (état végétatif), les crises d'épilepsie ou le somnambulisme (conscience<éveil) (Laureys, 2005a).

La perception consciente comporte deux versants: le niveau et le contenu (Overgaard et Overgaard, 2010). Le premier se rapporte à la question : « cette personne est-elle consciente ? » (forme intransitive) alors que le second porte sur la question: « cette personne est consciente, mais de quoi est-elle consciente exactement ? » (forme transitive). Dans ce travail, nous nous intéresserons principalement au niveau de conscience puisque nous étudions les états de conscience altérée après un coma (alors que les travaux sur le contenu vont s'orienter vers l'étude de sujets sains dans des conditions particulières). Le niveau de conscience peut donc se caractériser par la conscience d'un flux toujours changeant d'états mentaux spécifiques et donc une sorte d'exploration aléatoire du répertoire potentiel disponible alors que les contenus de la conscience sont ces états transitoires dont nous sommes conscients à chaque instant (Sadaghiani *et al.*, 2010).

Enfin, le contenu de la conscience peut à nouveau être divisé en deux composantes : la conscience interne et la conscience externe. La conscience externe ou de l'environnement est associée à une expérience vécue au travers des différentes modalités sensorielles. Le réseau neuronal impliqué dans la conscience de l'environnement comprend le cortex fronto-pariétal-cingulaire, prédominant dans les parties latérales (Boly *et al.*, 2007a; Vanhaudenhuyse & Demertzi *et al.*, 2011). La conscience interne se réfère aux processus mentaux qui ne requièrent pas la médiation de stimuli sensoriels externes, comme par exemple les pensées spontanées, le discours intérieur, la rêverie ou l'imagerie mentale (Lieberman, 2007). Le réseau neuronal impliqué dans la conscience de soi comprend le réseau du mode par défaut (Northoff *et al.*, 2006).

Plusieurs théories de la conscience ont vu le jour dans le domaine des neurosciences et postulent que la conscience émerge grâce à une ré-entrance (Lamme et Roelfsema, 2000), une diffusion globale (Dehaene et Naccache, 2001; Baars, 2005), et une intégration (Tononi, 2008) de l'information traitée par le cerveau. La présence d'une conscience nécessiterait une activité neurale ré-entrante, c'est-à-dire la transmission d'un signal neural retournant des cortex associatifs de haut niveau vers les modules de base. Il y aurait donc un échange bidirectionnel de l'information. Les activités ré-entrantes au sein de boucles cortico-corticales ou thalamo-corticales ont été décrites comme formant un noyau dynamique (*dynamic core*) (Edelman *et al.*, 2011) permettant le maintien de patterns synchrones dans le temps, à même

de connecter et d'intégrer des modules cognitifs distincts supportés par différentes aires cérébrales (Tononi et Edelman, 1998). La théorie de l'espace de travail neuronal global (*global neuronal workspace*) propose également une architecture qui associe un système cognitif modulaire avec l'idée que la conscience est avant tout déterminée par ses propriétés intégratives (Baars, 2005). La diffusion de l'information dans un espace neuronal global, comprenant les cortex fronto-pariétaux, permettrait l'état conscient (Dehaene et Naccache, 2001; Dehaene *et al.*, 2006). Quant à la théorie de l'intégration de l'information (Tononi, 2008), chaque expérience consciente est d'une part différenciée, c'est-à-dire reconnaissable parmi une multitude d'autres expériences possibles (répertoire d'information), et d'autre part intégrée, c'est-à-dire unifiée et non réductible à la somme de ses parties. L'unité de l'expérience consciente implique l'existence d'interactions causales au sein du cerveau. Cette théorie propose une mesure mathématique de Φ qui permet de mesurer le niveau de conscience à partir de la structure et des dynamiques d'un système donné. Un Φ élevé requiert un réseau de neurones comprenant à la fois une spécialisation fonctionnelle (chaque élément a un rôle fonctionnel unique dans le réseau) et une intégration fonctionnelle (présence de nombreuses voies d'interactions entre les éléments). Ce type d'architecture est caractéristique du système cortico-thalamique humain normal (l'architecture cérébelleuse n'est quant à elle pas favorable à l'intégration de l'information, ce qui corrèle avec la faible contribution de cette structure pour les corrélats neuraux de la conscience, Balduzzi et Tononi, 2008). Si cette architecture de connectivité est sévèrement perturbée, une perte de conscience sera observée (perte de connectivité effective, c'est-à-dire l'interaction causale entre différents modules cérébraux censée opérationnaliser l'intégration de l'information). Ces processus sont typiquement observés dans le sommeil profond, l'anesthésie, l'éveil non-répondant ou encore les absences épileptiques (Tononi et Koch, 2008). L'ensemble des idées proposées amène donc à l'hypothèse d'un syndrome de déconnexion chez les patients en état de conscience altérée (Laureys, 2005a; Tononi, 2010; Dehaene et Changeux, 2011).

1.2 Etats de conscience altérée

Classiquement, après une lésion cérébrale aiguë qui peut être d'origine traumatique (ex : accident de roulage) ou non-traumatique (ex : arrêt cardiaque), le patient perd connaissance et tombe dans le coma. Si les lésions sont trop importantes, le patient décède dans les jours qui suivent (mort cérébrale). Si le patient ouvre les yeux, il sort du coma et évolue vers un syndrome d'éveil non-répondant (état végétatif). Le patient reprend alors

graduellement une activité consciente (état de conscience minimale) qui se poursuit souvent par une période d'amnésie post-traumatique transitoire au cours de laquelle il reste confus. Dans la majorité des cas, le patient récupère en quelques semaines et peut ensuite entamer une prise en charge rééducative. Mais dans certains cas, le patient reste dans un état d'éveil non-répondant ou de conscience minimale (et plus rarement en locked-in syndrome) pendant plusieurs mois, voire plusieurs années ou décennies.

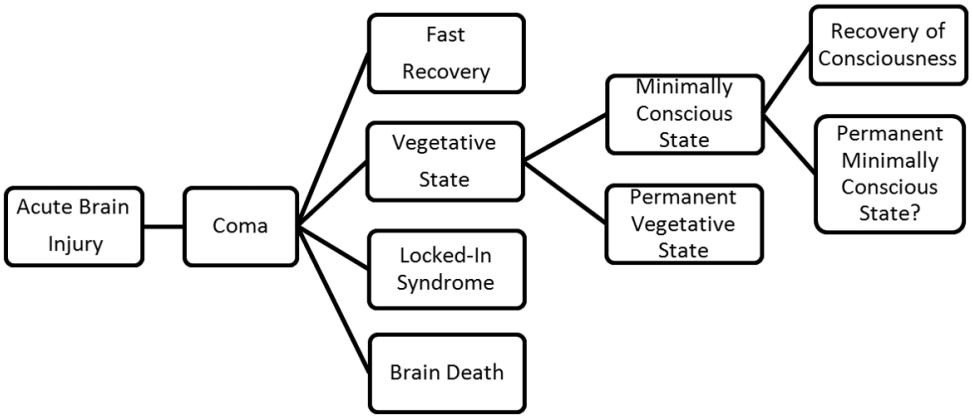


Figure 1: Evolution possible après une lésion cérébrale sévère. Noter que l'état de conscience minimale permanent n'est encore pas une entité clinique validée (Gosseries *et al.*, 2011d).

1.2.1 Mort cérébrale

Depuis le développement des techniques de respiration artificielle dans les années 50, la définition de mort clinique est passée d'une mort cardiaque, définie par une cessation irréversible des fonctions respiratoires et cardiaques, à une mort cérébrale. La mort cérébrale, ou le coma dépassé, implique la perte irréversible de toutes les fonctions cérébrales, indépendamment d'une ventilation et d'une circulation artificielles (Bernat, 2009). Le diagnostic de mort cérébrale est donc basé sur la perte définitive de tous les réflexes du tronc cérébral, une absence continue de respiration mise en évidence grâce à un test d'apnée, un coma démontré comme étant profond et non réactif à des stimuli nociceptifs, et l'exclusion de facteurs confondants tels que des troubles hypothermiques, médicamenteux, électrolytiques ou endocriniens (Wijdicks, 2001; Laureys, 2005b; Bernat, 2009). Des mouvements ralentis et provoqués par une activité spinale résiduelle peuvent toutefois être observés chez un tiers de ces patients (Saposnik *et al.*, 2000). Ils ne présentent cependant jamais d'expression faciale ni de vocalisation. Une réévaluation dans les 6 à 24 heures est recommandée afin de confirmer le diagnostic (The Quality Standards Subcommittee of the American Academy of Neurology, 1995; Wijdicks, 2001). L'absence d'activité cérébrale électrique par électroencéphalographie

(EEG) ou l'absence de flux sanguin cérébral par scintigraphie cérébrale ou angiographie peuvent également servir de confirmation (Laureys *et al.*, 2004a). Aucun patient diagnostiqué correctement en mort cérébrale n'a jamais récupéré (Bates *et al.*, 1977).

1.2.2 Coma

Le coma se caractérise par une absence totale d'ouverture des yeux et une absence de conscience de soi et de l'environnement (Teasdale et Jennett, 1974). Le patient comateux n'est donc ni éveillé, ni conscient. Cette pathologie résulte d'une atteinte importante du tronc cérébral, affectant particulièrement les systèmes réticulaires activateurs, et du cortex cérébral (Plum et Posner, 1983). La durée minimum du coma est d'une heure pour le différencier de la syncope, et peut durer jusqu'à quelques semaines dans les cas de comas pharmacologiques. Les fonctions autonomes (respiration, thermorégulation, régulation cardiovasculaire, etc.) sont diminuées, ce qui nécessite une aide respiratoire sous forme d'intubation ou de trachéotomie (Laureys *et al.*, 2001). Le patient en coma n'émet aucune production verbale et ne présente aucune réponse volontaire, même si des activités réflexes persistent et s'il peut parfois réagir à des stimulations douloureuses par des flexions ou des extensions des membres. Pour les comas d'origine non-traumatique, un mauvais pronostic peut être posé dans les trois jours à l'aide de marqueurs tels qu'une absence bilatérale de potentiels évoqués somesthésiques ou un taux trop élevé d'énolase neurospécifique (Boveroux *et al.*, 2008b). La moitié des patients qui ne récupèreront pas décèderont durant cette courte période (Schnakers *et al.*, 2004). En général, les patients qui survivent évoluent dans les deux à quatre semaines en passant par différents stades avant de récupérer partiellement ou complètement une conscience normale.

1.2.3 Syndrome d'éveil non-répondant (état végétatif)

Cet état pathologique, appelé auparavant syndrome apallique (Kretschmer, 1940) ou coma vigile (Calvet et Coll, 1959), se caractérise par une ouverture des yeux en absence de toute conscience de soi ou de l'environnement (The Multi-Society Task Force on PVS, 1994b). Les fonctions autonomes sont préservées et la respiration s'effectue généralement sans assistance technique. Ces patients ne présentent ni verbalisation intelligible, ni réponse volontaire mais ils peuvent manifester une variété de mouvements réflexes tels que grincer des dents, bouger les yeux, avaler, bailler, pleurer et sourire (Laureys, 2007). L'espérance de vie globale varie entre deux et cinq ans, rares sont les patients qui restent plus de dix ans dans cet état (The Multi-Society Task Force on PVS, 1994b). Un mois après l'accident, on parle d'« état végétatif persistant ». Après 3 mois (ou 6 mois chez les anglo-saxons) lorsque

l'étiologie est non-traumatique et après 12 mois lorsque l'étiologie est traumatique, on parle alors d'« état végétatif permanent » (Jennett, 1972; 1995). Le terme « persistant » renvoie à une certaine chronicité et implique un pronostic pessimiste quant à une possible récupération. Cette terminologie confond le diagnostic et le pronostic ce qui induit le risque potentiel que certains soins, comme par exemple le transfert vers un centre de réadaptation fonctionnelle, leur soient refusés. De même, le terme « permanent » insinue une quasi-absence de récupération et peut dès lors donner lieu à de graves décisions concernant l'arrêt des soins. Pourtant, une récupération est toujours possible, bien que la probabilité soit infime. Pour ces raisons, il est préférable de ne pas utiliser ces deux étiquettes, qui sont d'ailleurs toutes deux abrégées « PVS » (*persistant/permanent vegetative state*) et de parler plutôt en terme de durée exprimée en mois. En outre, un nouveau terme a été récemment proposé : le « syndrome d'éveil non-répondant » (*unresponsive wakefukness syndrome* - Laureys *et al.*, 2010) afin d'éviter la connotation négative intrinsèque du terme commun « végétatif » (comparant les patients à des végétaux) mais également parce que les fonctions cognitives résiduelles de ces patients peuvent être sous-estimées (à l'extrême, ils sont potentiellement conscients sans être en mesure de communiquer). Ce nouveau terme illustre adéquatement le fait que ces patients soient éveillés mais qu'ils ne présentent que des comportements réflexes qui ne sont aucunement liés à une réponse volontaire (Gosseries & Bruno *et al.*, 2011b). Dans ce travail, nous réfèrerons donc ces patients à ce dernier terme essentiellement, en parlant de *patients en état d'éveil non-répondant*.

1.2.4 Etat de conscience minimale

L'état de conscience minimale est une entité clinique plus récente qui se manifeste par des signes de conscience élémentaires et fluctuants. Ces patients sont capables de répondre à un ordre verbal ou écrit, d'émettre des verbalisations intelligibles, de suivre visuellement du regard et de localiser des stimulations nociceptives (American Congress of Rehabilitation Medicine, 1995; Giacino *et al.*, 2002). Ils présentent également des comportements émotionnels appropriés tels que des sourires, des rires ou des pleurs. Bien que ces réponses soient fluctuantes, elles doivent être reproductibles pour pouvoir conclure que l'action est volontaire. Les patients sont donc éveillés et leur conscience fluctue mais ils restent incapables de communiquer de manière fonctionnelle et donc d'exprimer leurs pensées. Le pronostic des patients en état de conscience minimale est meilleur que celui des patients en état d'éveil non-répondant (Noé *et al.*, 2012). Très récemment, l'état de conscience minimale

a été sous-divisé en « état de conscience minimale moins - » qui se caractérise par des signes primaires de conscience qui ne relèvent pas du langage (ex : poursuite visuelle) et en « état de conscience minimale plus + » qui se définit par la présence d'une compréhension verbale (Bruno & Vanhaudenhuyse *et al.*, 2011; Bruno *et al.*, 2011). Tout comme le syndrome d'éveil non-répondant, l'état de conscience minimale peut être un état transitoire, chronique ou permanent (Laureys, 2007). Cependant, il n'existe actuellement aucun critère permettant de parler d'état de conscience minimale permanent. Dès le moment où le patient est capable de communiquer de manière fonctionnelle ou d'utiliser adéquatement des objets, il est considéré comme émergeant de l'état de conscience minimale (Giacino *et al.*, 2002).

1.2.5 Locked-in syndrome

Le locked-in syndrome, ou syndrome de verrouillage, n'est pas à proprement parler un état de conscience altérée mais peut facilement être confondu avec les autres entités mentionnées. Ce syndrome de dé-efférentiation, encore appelé pseudocoma ou syndrome d'enfermement, se caractérise par une tétraplégie et une anarthrie résultant d'une interruption respective des voies cortico-spinales et cortico-bulbaires (American Congress of Rehabilitation Medicine, 1995). Dans plus de 50% des cas, l'étiologie est d'origine vasculaire (thrombose occlusive de l'artère basilaire ou hémorragie pontique) mais elle peut également être traumatique (Laureys *et al.*, 2005a). Bien que ces patients ne puissent pas bouger, leurs sensations restent intactes et ils sont tout à fait conscients. Ils peuvent toutefois bouger les yeux et retrouvent généralement un certain contrôle distal comme des mouvements des doigts, des orteils ou de la tête (à l'exception des patients en locked-in syndrome complet qui présentent une immobilité complète incluant les mouvements oculaires). Le principal moyen de communication se réalise donc via le mouvement des yeux et parfois avec l'extrémité d'un doigt (Bauby, 1997). Le patient peut répondre aux questions par un code élémentaire comme cligner des yeux une fois pour « oui » et deux fois pour « non », ou bouger le doigt une fois pour « oui » et deux fois pour « non ». D'autres moyens de communication plus élaborés permettent une meilleure communication comme l'utilisation de l'alphabet ESARINT (basé sur la fréquence d'apparition des lettres dans la langue française) ou l'utilisation d'un ordinateur incluant une caméra qui détecte les mouvements oculaires (Gosseries *et al.*, 2009). Les fonctions cognitives de ces patients sont totalement préservées si la lésion ne se situe qu'au niveau du tronc cérébral. Si des lésions corticales additionnelles sont présentes, les fonctions cognitives associées à ces aires corticales seront altérées (Schnakers *et al.*, 2008c).

Contrairement à la croyance populaire, la qualité de vie de ces patients ne semble pas plus faible que celle de la population générale lorsqu'elle est évaluée subjectivement (Laureys *et al.*, 2005a; Bruno & Bernheim *et al.*, 2011).

1.3 Evaluation clinique

Sur le plan de la revalidation neurologique, l'évaluation du niveau de conscience revêt une grande importance en raison des implications en termes de pronostic et de décisions thérapeutiques mais également aux niveaux médico-légal et éthique (Demertzi *et al.*, 2008). L'évaluation comportementale reste la méthode de base pour réaliser un diagnostic d'état de conscience au chevet du patient (Majerus *et al.*, 2005). Les études cliniques réalisées dans les années 90 ont illustré la difficulté qu'il existe à différencier un comportement réflexe d'un comportement volontaire, menant à des erreurs diagnostiques dans 40% des cas (Andrews *et al.*, 1996; Childs et Mercer, 1996). En effet, les déficits moteurs, langagiers et les troubles de la vigilance sont autant de facteurs pouvant entraver les réponses du patient lors de l'évaluation clinique. Une étude récente a mis en évidence que ce taux d'erreurs diagnostiques reste actuellement inchangé lorsque le diagnostic est réalisé sans l'appui d'échelles standardisées sensibles, et ce, malgré l'introduction des critères diagnostiques de l'état de conscience minimale (Schnakers *et al.*, 2009b).

Parmi les échelles comportementales, la Glasgow Coma Scale (échelle de référence internationale - Teasdale et Jennett, 1974), la Glasgow Liège Scale (évalue en plus les réflexes du tronc cérébral - Born *et al.*, 1982) et plus récemment, l'échelle Full Outline of UnResponsiveness (Wijdicks *et al.*, 2005) sont généralement utilisées chez les patients au stade aigu. Pour les patients au stade chronique, on retrouve l'échelle de récupération du coma (Coma Recovery Scale-Revised – CRS-R, Giacino *et al.*, 2004; Schnakers *et al.*, 2008b), la Wessex Head Injury Matrix (Majerus et Van der Linden, 2000; Shiel *et al.*, 2000), la Sensory Modality Assessment and Rehabilitation Technique (Gill-Thwaites et Munday, 2004), la Western Neuro Sensory Stimulation Profile (Ansell et Keenan, 1989), la Disability Rating Scale, ou encore la Near Coma Scale (Rappaport, 2005). Une récente méta-analyse (Seel *et al.*, 2010) préconise l'utilisation de l'échelle de récupération du coma (CRS-R) pour évaluer le niveau de conscience des patients. Pour les patients au stade aigu, nous recommandons l'utilisation de l'échelle Full Outline of UnResponsiveness (Schnakers *et al.*, 2006; Bruno & Ledoux *et al.*, 2011). Ces deux échelles offrent en effet l'avantage de rechercher systématiquement la présence de comportements non réflexes (ex : poursuite visuelle, réponse

orientée suite à une stimulation nociceptive) en plus de réponses volontaires suite à une commande verbale. Les patients inclus dans les différentes études de ce travail ont été diagnostiqués sur base de l'évaluation clinique réalisée à l'aide de la CRS-R. Cette échelle évalue six composantes: l'audition, la vision, la motricité, les fonctions oro-motrices et verbales, la communication et l'éveil. Vingt-trois items sont ordonnés selon leur degré de complexité; les items les moins complexes de chaque sous-échelle représentent des comportements réflexes alors que les items les plus complexes représentent des comportements conscients. Le diagnostic se base sur la présence (ou l'absence) de comportements opérationnels en réponse à des stimulations sensorielles spécifiques (par exemple, si une poursuite visuelle est présente au moins 2 fois dans la même direction, le patient est considéré comme étant en état de conscience minimale). En outre, la poursuite visuelle devrait être évaluée au moyen d'un miroir, et non d'un objet ou d'une personne (Vanhaudenhuyse *et al.*, 2008b). Nous avons également montré que le réflexe de clignement à la menace et la fixation visuelle ne reflètent pas nécessairement des comportements conscients (Vanhaudenhuyse *et al.*, 2008a; Bruno *et al.*, 2010b).

Enfin, l'absence de réaction comportementale n'étant pas une preuve absolue d'absence de conscience, il est essentiel de réaliser des évaluations répétées et approfondies avec des personnes expertes dans le domaine (Godbolt *et al.*, 2012). Des facteurs confondants tels que l'effet sédatif de certains médicaments, la présence d'infections, et les complications médicales doivent également être pris en compte lors de l'évaluation clinique de la conscience. Cette situation est encore plus problématique lorsque les patients présentent des déficits cognitifs tels que l'aphasie, l'agnosie ou l'apraxie (Majerus & Bruno *et al.*, 2009). Malgré des examens cliniques réalisés dans les meilleures conditions possibles, certains patients peuvent toutefois encore être sous-estimés en terme de cognition et de conscience résiduelles (Laureys et Boly, 2007), notamment parce que nous sommes limités à l'observation de comportements moteurs liés à la conscience de l'environnement. Grâce au développement des techniques de neuroimagerie, ce problème peut être adressé en évaluant l'étendue des lésions structurelles cérébrales mais surtout en mesurant l'activité cérébrale au repos, lors de stimulations sensorielles passives et pendant des tâches d'imagerie mentale (Gosseries & Bruno *et al.*, 2011a).

1.4 Evaluation par neuroimagerie

1.4.1 Mesures des lésions structurelles

Malgré les avancées en neuroimagerie structurelle, quelques travaux seulement se sont portés sur les bases neuroanatomiques à l'origine des troubles de la conscience. Les études neuropathologiques *post-mortem* ont montré la présence de lésions axonales diffuses chez les patients en état de conscience altérée (Kinney et Samuels, 1994; Adams *et al.*, 1999; Jennett *et al.*, 2001). Des études plus récentes *in vivo,* utilisant l'imagerie par tenseur de diffusion, ont confirmé la présence d'une altération étendue de la matière blanche chez ces patients (Tshibanda & Vanhaudenhuyse *et al.*, 2010), avec des différences selon le diagnostic (Fernández-Espejo *et al.*, 2011), l'étiologie (Newcombe *et al.*, 2010) et la récupération fonctionnelle successive (Perlbarg *et al.*, 2009; Tollard *et al.*, 2009). Les altérations de la matière blanche sous-corticale et du thalamus semblent plus importantes chez les patients en état d'éveil non-répondant que chez ceux en état de conscience minimale (Fernández-Espejo *et al.*, 2011). Une étude de cas rapporte une repousse axonale étonnante dans les régions précunéales chez un patient ayant émergé de l'état de conscience minimale après 19 ans (Voss *et al.*, 2006). Une autre étude n'a cependant pas pu mettre en évidence une telle amélioration de la matière blanche chez un patient ayant récupéré un niveau de conscience normal un an après l'accident cérébral (Fernandez-Espejo *et al.*, 2010). De plus, certains patients présentent une relative préservation de la matière blanche tout en ayant de sévères déficits fonctionnels (Bruno & Fernández-Espejo *et al.*, 2011). Ces résultats disparates nous amènent donc à nous orienter vers l'étude fonctionnelle du cerveau au moyen de techniques telles que la tomographie par émissions de positons (TEP) et l'imagerie par résonance magnétique fonctionnelle (IRMf).

1.4.2 Mesure de l'activité cérébrale au repos

Historiquement, les premières études mesurant le métabolisme cérébral réalisées au moyen de la TEP (technique invasive qui utilise un marqueur radioactif – le fluorodésoxyglucose 18 – pour mesurer la consommation de glucose au niveau cérébral) ont montré une diminution globale importante chez les patients en état d'éveil non-répondant comparés à des sujets sains éveillés. Cette diminution métabolique cérébrale varie de 25 à 72% selon les études (tableau 1) (Levy *et al.*, 1987; De Volder *et al.*, 1990; Tommasino, 1994; Laureys *et al.*, 1999b; Rudolf *et al.*, 1999). Il a ensuite été montré que ces patients

présentent plus particulièrement un déficit métabolique au niveau du réseau fronto-pariétal et du thalamus (Laureys *et al.*, 1999a; 2000b; Rudolf *et al.*, 2000; Tengvar *et al.*, 2004; Beuthien-Baumann *et al.*, 2005; Juengling *et al.*, 2005; Nakayama *et al.*, 2006; Lull *et al.*, 2010) (tableau 1) alors que les structures sous-corticales et le tronc cérébral restent relativement préservés (Laureys *et al.*, 2002a; Silva *et al.*, 2010). Ce réseau fronto-pariétal comprend les aires associatives médiales (cortex mésiofrontal/cingulaire antérieur et cortex cingulaire postérieur/précuneus) et latérales (cortex préfrontal et pariétal postérieur). Récemment, un classificateur automatique a été développé pour évaluer l'intégrité fonctionnelle de ce réseau fronto-pariétal et pour calculer la probabilité d'être en état d'éveil non-répondant ou en locked-in syndrome, en se basant sur des résultats obtenus en TEP (Phillips *et al.*, 2011). Des études chez des sujets sains éveillés, en sommeil et en anesthésie générale ont également confirmé le rôle du réseau fronto-pariétal dans la genèse de la conscience (Dehaene, 2000; Rees *et al.*, 2002; Boveroux *et al.*, 2008a; Maquet, 2010). Au sein de ce réseau, le précuneus/cortex cingulaire postérieur semble jouer un rôle primordial puisqu'il est le plus actif en condition de repos (Vogt et Laureys, 2005; Cavanna et Trimble, 2006; Raichle et Snyder, 2007) et semble être la région la plus endommagée chez les patients en état de conscience altérée (Laureys *et al.*, 2005c). De plus, la récupération de conscience a été corrélée à la récupération métabolique dans cette région particulière (Laureys *et al.*, 1999b; 2006). Enfin, une restauration des connexions entre le réseau fronto-pariétal et le thalamus a également été démontrée lors de la récupération de conscience chez un patient en état d'éveil non-répondant (Laureys *et al.*, 2000b). Le rôle des projections thalamiques dans la conscience a été confirmé par une étude de stimulation cérébrale profonde chez un patient en état de conscience minimale (Schiff *et al.*, 2005).

Plus récemment, l'activité cérébrale au repos a pu être évaluée au moyen de l'IRMf qui mesure les changements hémodynamiques, et qui, en comparaison à la TEP, est non ionisante et présente une meilleure résolution temporelle (seconde au lieu de minute) (Gosseries *et al.*, 2008). L'IRMf a permis d'étudier plus amplement un réseau en particulier, le réseau du mode par défaut (initialement mesuré avec la TEP - Raichle *et al.*, 2001), qui s'active lorsque nous sommes éveillés et au repos, et qui se désactive lors de tâches orientées vers un but (Boly *et al.*, 2008b). Ce réseau semble particulièrement impliqué dans les processus internes tels que les pensées spontanées, le discours intérieur, la mémoire épisodique ou les représentations de soi (Goldberg *et al.*, 2006; Laureys *et al.*, 2007; Soddu *et al.*, 2009). Il comprend des régions cérébrales telles que le cortex cingulaire postérieur, le

précunéus, les jonctions temporo-pariétales et le cortex préfrontal. De manière consistante, aucun réseau du mode par défaut n'a pu être détecté chez un patient en mort cérébrale (Boly *et al.*, 2009; Soddu *et al.*, 2011), et une diminution de l'activité de ce réseau a été observée chez des patients en état d'éveil non-répondant (Boly *et al.*, 2009; Cauda *et al.*, 2009). Les patients en état de conscience minimale ont quant à eux montré un pattern d'activation plus similaire à celui observé chez les sujets contrôles (Bruno & Fernández-Espejo *et al.*, 2011; Soddu *et al.*, 2012), avec notamment une connectivité fonctionnelle plus importante au niveau du précuneus/cortex cingulaire postérieur par rapport aux patients en état d'éveil non-répondant. Le niveau de connectivité fonctionnelle au sein de ce réseau du mode par défaut semble donc corrélé au niveau de conscience des patients (Vanhaudenhuyse & Noirhomme *et al.*, 2010). Ces données ont été confirmées récemment par une étude en TEP qui montre une récupération progressive du métabolisme cérébral de ce réseau interne en fonction du niveau de conscience des patients (Thibaut & Bruno *et al.*, 2012).

Reference	N	Diagnosis	Etiology	Duration	Main findings
A. PET					
Levy et al., 1987	7	VS/UWS	TBI/NTBI	1–72 m	60% (53–67%) decrease in metabolism
De Volder et al., 1990	7	VS/UWS	NTBI	1–4 m	53% (43–65%) decrease in metabolism
Tommasino et al., 1995	10	VS/UWS	TBI/NTBI	2–24 m	56% decrease in metabolism
Rudolf et al., 1999	24	VS/UWS	NTBI	< 1 m–6 m	25% decrease in metabolism (17% < 3 m and 33% > 3 m)
Laureys et al., 1999	1	VS/UWS	NTBI	1 m	38% decrease in metabolism; recovery of consciousness = FP recovery
Laureys et al., 1999	4	VS/UWS	TBI/ NTBI	< 1 m–60 m	FP hypometabolism & disconnections
Laureys et al., 2000	1	VS/UWS	NTBI	4 m	recovery of consciousness = thalamocortical reconnections
Rudolf et al., 2000	9	VS/UWS	NTBI	< 1 m	decrease in benzodiazepine receptor density
Laureys et al., 2002	30	VS/UWS	TBI/ NTBI	1–5 m	56% (37–72%) decrease in metabolism
Beuthien-Baumann, 2003	16	VS/UWS	TBI	2–12 m	58% decrease in metabolism; FP hypometabolism
Tengvar, 2004	1	MCS	NTBI	6 m	47–65% FP hypometabolism
Juengling et al., 2005	5	VS/UWS	NTBI	1–48 m	FP and thalamus hypometabolism
Nakayama et al., 2006	30	17 VS/UWS 13 MCS	TBI	6–60 m	FP and thalamus hypometabolism in VS/UWS, less impaired in MCS
Silva et al., 2010	10	VS/UWS	TBI/ NTBI	2–24 m	FP hypometabolism
Lull et al., 2010	17	VS/UWS & MCS	TBI	12 m	thalamus hypometabolism
Bruno et al., 2010	10	VS/UWS	NTBI	3 m	FP hypometabolism (VS/UWS without fixation = "MCS" with fixation)
B. fMRI					
Boly et al., 2009	1	VS/UWS	NTBI	36 m	FP disconnections
Cauda et al., 2009	3	VS/UWS	TBI/NTBI	20 m	FP disconnections
Vanhaudenhuyse et al., 2010	13	4 VS/UWS & 5 coma 4 MCS	TBI/NTBI	< 1 – 60 m	FP disconnections correlate with consciousness level

Note. N = Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; FP = frontoparietal associative network; TBI = traumatic brain injury; NTBI = non traumatic brain injury; m = months.

Tableau 1. Résultats principaux des études du fonctionnement cérébral au repos chez les patients en état d'éveil non-répondant (VS/UWS) et en état de conscience minimale (MCS) par TEP et IRMf (Gosseries & Bruno *et al.*, 2011b).

1.4.3 Mesure de l'activité cérébrale en réponse à des stimulations sensorielles

Fin des années 90, c'est à l'aide de la TEP marquée à l'^{15}O que les études d'activation ont pu mesurer l'augmentation régionale du flux sanguin cérébral en réponse à des stimulations externes passives auditives, visuelles et sensorielles. Ces études ont principalement montré qu'en réponse à des stimuli externes, les patients en état d'éveil non-répondant présentent une activité cérébrale de bas niveau c'est-à-dire uniquement dans les cortex sensoriels primaires. Ces activations restent fonctionnellement déconnectées de l'ensemble du réseau fronto-pariétal (Menon *et al.*, 1998; Laureys *et al.*, 2000a; 2002b; Schiff *et al.*, 2002; Boly *et al.*, 2004; Giacino *et al.*, 2006; Owen *et al.*, 2006). La préservation de ces îlots d'activation a ensuite été confirmée par des études en IRMf (Bekinschtein *et al.*, 2005; Fernandez-Espejo *et al.*, 2008; Rousseau *et al.*, 2008; Heelmann *et al.*, 2010) (tableau 2). Certaines études ont cependant montré un pattern d'activation de plus haut niveau, c'est-à-dire une activation cérébrale étendue aux cortex associatifs multimodaux chez certains patients en état d'éveil non-répondant (de Jong *et al.*, 1997; Moritz *et al.*, 2001; Kassubek *et al.*, 2003; Owen *et al.*, 2005; Staffen *et al.*, 2006) (tableau 2). D'autres études ont également montré la valeur pronostique de tels résultats (Di *et al.*, 2008; Coleman *et al.*, 2009). Ce type d'activation de haut niveau est fréquemment rencontré, quoique de manière non systématique, chez les patients en état de conscience minimale et est similaire à celui observé chez des sujets sains (Bekinschtein *et al.*, 2004; Boly *et al.*, 2008a; Zhu *et al.*, 2009; Qin *et al.*, 2010). En effet, suite à des stimulations auditives ou nociceptives, les études démontrent une activation cérébrale plus étendue chez les patients en état de conscience minimale, ainsi qu'une augmentation des connexions fonctionnelles cortico-corticales à longue distance dans le réseau fronto-pariétal par rapport aux patients en état d'éveil non-répondant (Boly *et al.*, 2004; 2008a). Ces résultats suggèrent que les patients en état de conscience minimale perçoivent les stimulations auditives et nociceptives. De plus, chez ces patients, des stimuli auditifs ayant une valence émotionnelle (ex : cris d'un bébé, récit narré par la mère du patient, prénom du patient) induisent une activité cérébrale significativement plus étendue que des stimuli neutres (Laureys *et al.*, 2004c; Schiff *et al.*, 2005; Di *et al.*, 2007). Notons toutefois que l'activation d'une aire cérébrale ne constitue pas une preuve absolue de conscience et pourrait dans certains cas être considérée comme un mécanisme automatique.

Ces données de neuroimagerie nous invitent à quelques considérations concernant la pratique clinique. D'une part, en tant que cliniciens, nous devons être prudents lorsque nous nous adressons aux patients en état de conscience minimale et d'autre part, le traitement

analgésique de ces patients ne doit pas être négligé. La « Nociception Coma Scale » a, par ailleurs, été récemment proposée pour évaluer les signes de douleurs chez ces patients incapables de communiquer (Schnakers *et al.*, 2010a; 2010b). Et comme mentionné précédemment, le risque de diagnostic erroné étant encore élevé, ces recommandations devraient être appliquées à tous les patients récupérant du coma.

References	Etiology	Duration	N	Diagnostic	Modality	Level of activation
A. PET						
De Jong et al., 1997 [27]	TBI	2 m	1	VS/UWS	auditory (familiar voice)	high
Menon et al., 1998 [72]	NTBI	3 m	1	VS/UWS	visual (familiar face)	low
Schiff et al., 2002 [90]	TBI/NTBI	6–300 m	5	3 VS/UWS	auditory (click), tactile	low
				2 VS/UWS		high
Owen et al., 2002 [78]	TBI/NTBI	4 m	3	1 VS/UWS	visual (familiar face), auditory (noise, words)	low
				2 VS/UWS		high
Laureys et al., 2002 [60]	TBI/NTBI	1 m	15	VS/UWS	pain (electrical stimulation)	low
Kassubek et al., 2003 [45]	NTBI	3–48 m	7	VS/UWS	pain (electrical stimulation)	high
Boly et al., 2004 [13]	TBI/NTBI	1–4 m	20	15 VS/UWS	auditory (click)	low
				5 MCS		high
Laureys et al., 2004 [65]	NTBI	6 m	1	MCS	auditory (noise, cries, own name)	high
Owen et al., 2005 [77]	NTBI	4 m	1	VS/UWS	auditory (speech)	high
Giacino et al., 2006 [37]	TBI/NTBI	1–3 m	5	VS/UWS	visual (flash)	low
Boly et al., 2008 [14]		1–4 m	15	VS/UWS	pain (electrical stimulation)	low
			5	MCS		high
Silva et al., 2010 [98]	TBI/NTBI	2–22 m	10	VS/UWS	tactile	low
B. fMRI						
Moritz et al., 2001 [74]	TBI	< 1 m	1	VS/UWS	tactile, visual (flash), auditory (speech)	high
Bekinschtein et al., 2004 [7]	TBI	5 m	1	MCS	auditory (familiar voice)	high
Bekinschtein et al., 2005 [9]	TBI	2 m	1	VS/UWS	auditory (words)	low
Schiff et al., 2005 [91]	TBI/NTBI	18 m	2	MCS	auditory (speech), tactile	high
Owen et al., 2006 [76]	TBI	6 m	1	VS/UWS	auditory (speech, ambiguity), visual	high
Staffen et al., 2006 [100]	NTBI	10 m	1	VS/UWS	auditory (own name)	high
Di et al., 2007 [32]	TBI/NTBI	2–48 m	11	5 VS/UWS	auditory (familiar voice own name)	low
				2 VS/UWS		high
				4 MCS		high
Coleman et al., 2007 [26]	TBI/NTBI	9–108 m	12	4 VS/UWS	auditory (forward/backward speech, ambig-uity)	low
				3 VS/UWS		high
				5 MCS		low/high
Fernandez-Espejo et al., 2008 [34]	TBI	1–11 m	7	2 VS/UWS	auditory (forward/backward speech)	low
				1 VS/UWS		high
				4 MCS		low/high
Rousseau et al., 2008 [84]	NTBI	60 m	4	VS	tactile, visual and auditory	low
Coleman et al., 2009 [25]	TBI/NTBI	2–120 m	46	20 VS/UWS	auditory (forward/backward speech, ambi-	low
				7 VS/UWS	guity)	high
				19 MCS		low/high
Zhu et al., 2009 [113]	TBI/NTBI	1–2 m	9	MCS	visual (emotional picture)	high
Qin et al., 2010 [81]	TBI/NTBI	2–48 m	11	7 VS/UWS	auditory (familiar voice own name)	low
				4 MCS		high
Fernandez-Espejo et al., 2010 [33]	TBI	1 m	1	VS/UWS	auditory (speech forward/backward)	high
Heelman et al., 2010 [41]	TBI	< 2 m, >6 m	6	6 VS/UWS	visual (flash)	low
		14 m		1 MCS		high

Note. N = Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; FP = frontoparietal associative network; TBI = traumatic brain injury; NTBI = non traumatic brain injury; m = months.

Tableau 2. Niveau d'activation cérébrale en réponse à des stimulations sensorielles passives évaluées au moyen de la TEP ^{15}O et de l'IRMf chez les patients en état de conscience altérée (Gosseries & Bruno *et al.*, 2011b).

1.4.4 Communiquer sans parole ni geste via des paradigmes actifs

Parallèlement aux études de neuroimagerie fonctionnelle réalisées au repos et lors de stimulations sensorielles passives, des paradigmes dits « actifs » ont été développés récemment. Ils permettent d'obtenir une réponse à la commande chez des patients sévèrement cérébrolésés, grâce à l'activité cérébrale uniquement, sans l'intervention des canaux moteurs et langagiers classiques (Bruno & Soddu *et al.*, 2010). En effet, les tâches d'imagerie mentale activent des régions cérébrales spécifiques qui peuvent être détectés en IRMf (Boly *et al.*, 2007b; Sorger *et al.*, 2009). Par exemple, si l'on s'imagine jouer au tennis, le cortex prémoteur s'active alors que lorsque l'on s'imagine parcourir les pièces de sa propre maison, le cortex parahippocampique s'active. Une patiente diagnostiquée en état d'éveil non-répondant a présenté des activations robustes et spécifiques quand il lui a été demandé de réaliser ces deux tâches d'imagerie mentale. Cette patiente devait donc être consciente pour comprendre et effectuer les commandes demandées (Owen *et al.*, 2006). Ce paradigme a ensuite été appliqué chez 54 patients en état de conscience altérée et cinq d'entre eux ont montré une activité cérébrale consistante avec les tâches d'imagerie mentale (Monti & Vanhaudenhuyse *et al.*, 2010). Parmi ceux-ci, deux n'avaient jamais montré aucun signe comportemental de conscience. L'absence d'activation cérébrale ne permet cependant pas de conclure à une absence de conscience. En effet, la majorité des patients en état de conscience minimale inclus dans cette étude n'ont pas montré d'activation cérébrale dans les régions d'intérêt. Plus impressionnant encore, ce paradigme a été adapté en un système par réponse oui/non pour permettre à un patient en état de conscience minimale de communiquer via la modulation de son activité neuronale (Monti & Vanhaudenhuyse *et al.*, 2010). La présence d'une réponse à la commande via l'IRMf ne garantit cependant pas que le patient puisse utiliser ce moyen pour communiquer, comme démontré très récemment chez deux patients conscients sévèrement cérébrolésés (Bardin *et al.*, 2011). Ces paradigmes actifs en IRMf sont actuellement utilisés avec des méthodologies diverses chez les patients en état de conscience altérée. Il leur est par exemple demandé de 'regarder l'écran et de silencieusement nommer l'objet présenté' (produisant l'activation du réseau langagier) (Rodriguez Moreno *et al.*, 2010), de 'bouger la main' (activation du cortex prémoteur) (Bekinschtein *et al.*, 2011) ou de 's'imaginer nager' (activation de l'aire motrice supplémentaire) (Bardin *et al.*, 2011) avec notamment des propositions de classification de modèle (Bardin *et al.*, 2012). Enfin, des interfaces cerveau-ordinateur utilisant l'EEG sont également en cours de validation pour permettre une évaluation au chevet des patients (voir chapitre 3).

1.5 Objectifs de ce travail

Emettre un diagnostic d'état de conscience altérée chez les patients sévèrement cérébrolésés est essentiel afin de fournir aux équipes médicales des indications pronostiques mais également pour permettre d'adapter le traitement et de prendre des décisions adéquates concernant la revalidation ou la fin de vie (Gosseries *et al.*, 2011a). L'évaluation comportementale est la méthode de référence pour différencier ces patients. Elle se base sur les réponses motrices (volontaires et reproductibles) qui sont parfois difficiles à observer chez ces patients (Gosseries *et al.*, 2011d). Ces limites engendrent la nécessité de faire appel à des techniques paracliniques qui permettent des mesures plus objectives de l'état de conscience. Les études en IRM et TEP ont montré qu'il est possible de détecter des signes de conscience au travers de l'activité cérébrale, notamment chez des patients diagnostiqués en syndrome d'éveil non-répondant, et dans de rares cas, d'établir une communication de base grâce aux paradigmes actifs en IRMf (pour une revue, voir Gosseries & Bruno *et al.*, 2011b). Ces tâches d'imagerie mentale nécessitent cependant des capacités cognitives de haut niveau et peuvent être difficiles à effectuer pour les patients sévèrement cérébrolésés. En effet, de nombreux patients en état de conscience minimale (et en locked-in syndrome) sont incapables de réaliser ces paradigmes en raison de troubles cognitifs surajoutés, ce qui suscite donc des faux négatifs (Gosseries & Bruno *et al.*, 2011a). De plus, les techniques par IRM et TEP sont peu pratiques au quotidien puisqu'elles impliquent de déplacer les patients dans un milieu hospitalier pourvu de ces outils. Leur résolution temporelle semble également insuffisante pour capter la dynamique de la génération d'une activité neuronale consciente. En effet, elles sont des mesures indirectes de l'activité neuronale puisqu'elles évaluent l'oxygénation et le taux de glucose sanguin dans le cerveau (Gosseries *et al.*, 2008). La sensibilité et la sensitivité de ces techniques paracliniques ne sont donc pas suffisantes pour détecter des signes de conscience au niveau individuel en routine clinique.

L'EEG permet par contre de mesurer directement l'activité électrique neuronale, et ce, au chevet des patients. Dans le chapitre 3, nous introduirons cette technique et passerons en revue les principales études réalisées jusqu'à présent chez les patients en état de conscience altérée (Gosseries & Lehembre *et al.*, sous presse). Dans le but de dégager des biomarqueurs diagnostiques et pronostiques, nous testerons ensuite deux mesures électrophysiologiques : une mesure d'entropie automatisée facilement applicable en routine clinique et une mesure de potentiels évoqués auditifs nécessitant des analyses complexes (Gosseries & Schnakers *et al.*,

2011, Boly *et al.*, 2011a; 2011b;). La stimulation magnétique transcrânienne (SMT) est un autre outil paraclinique qui permet de stimuler directement le cerveau. Lorsqu'elle est appliquée sur le cortex moteur, les réponses périphériques musculaires peuvent être enregistrées pour évaluer les déficits moteurs. Le chapitre 4 présentera cette technique et résumera les quelques études effectuées chez les patients gravement cérébrolésés (Lapitskaya *et al.*, 2009a; 2009b). Nous évaluerons ensuite une série de mesures électromyographiques afin de mieux documenter les problèmes moteurs rencontrés chez nos patients et nous les corrélerons avec le niveau de conscience (Gosseries & Lapitskaya *et al.*, soumis). La SMT peut également être combinée à l'EEG afin d'investiguer directement l'effet de la stimulation sur l'activité électrique du cortex cérébral (Gosseries & Rosanova *et al.*, soumis). Nous utiliserons ce dernier outil novateur pour tenter de différencier au niveau individuel les patients en état d'éveil non-répondant des patients en état de conscience minimale (chapitre 5, Gosseries & Rosanova *et al.*, 2012). Parallèlement à ces études, nous aborderons également les difficultés psychologiques rencontrées par le personnel soignant et les familles lors de la prise en charge d'une personne sévèrement cérébrolésée et incapable de communiquer, ce qui fera l'objet du chapitre 6 (Gosseries *et al.*, accepté; soumis). Enfin le dernier chapitre synthétisera les résultats de nos études et proposera des perspectives futures dans une approche à la fois clinique mais également scientifique.

En effet, le premier versant de ce travail est, comme nous venons de le voir, de valider de nouveaux marqueurs paracliniques pour optimaliser l'exactitude du diagnostic (et du pronostic) des patients en état de conscience altérée. Le second versant est de parvenir à concilier nos données avec la littérature scientifique actuelle sur la conscience. La précision du diagnostic repose sur une meilleure compréhension des processus cérébraux nécessaires à l'émergence de la conscience. Il y a donc un grand intérêt à prendre en compte les approches théoriques qui tentent d'élucider un mécanisme cérébral général de la perception consciente (Tononi, 2008; Dehaene et Changeux, 2011). Les théories neuroscientifiques actuelles proposent que pour être conscient, le cerveau doit être capable de produire une information qui soit intégrée, et donc complexe. L'intégration de l'information résulterait en de nombreuses boucles ré-entrantes dans un espace global fronto-pariétal capable de diffuser l'information à des aires cérébrales distantes (Dehaene et Changeux, 2011). Les troubles de la conscience reflèteraient, dès lors, un syndrome de déconnexion cérébrale (Laureys, 2005a). La perte de conscience observée chez les patients sévèrement cérébrolésés peut donc être vue comme une perte d'intégration et de différentiation de l'activité neuronale (perte

d'information), avec une altération de la connectivité effective entre les différentes aires cérébrales (Tononi et Koch, 2008). La connectivité effective se réfère à la capacité de certains groupes neuronaux d'affecter de manière causale le taux de décharge d'autres groupes de neurones. Pour tester ces hypothèses, nous investiguerons d'abord la complexité cérébrale au moyen d'une mesure d'EEG-entropie afin de confirmer une perte de complexité cérébrale chez nos patients (section 3.2). Ensuite, nous évaluerons les connexions cortico-corticales au moyen de l'EEG (section 3.3) et de l'EEG-SMT (chapitre 5) afin de tester l'hypothèse de la perte de connectivité effective et du syndrome de déconnexion. Les connexions cortico-spinales seront également mesurées (chapitre 4). Nos études permettront ainsi d'améliorer le diagnostic différentiel d'état de conscience altérée, de clarifier l'activité cérébrale qui sous-tend un pattern de comportements considérés comme conscients et d'ajouter une pierre de plus à l'édifice de la quête pour les corrélats neuronaux de la conscience humaine.

La structure du présent travail se base sur les techniques employées (évaluation clinique, EEG, SMT, SMT-EEG). Dans le chapitre suivant, nous détaillerons une étude clinique réalisée aux Etats-Unis concernant le pronostic des patients en état de conscience altérée. Toutes les études rapportées dans ce travail ont reçu l'approbation d'un comité éthique hospitalo-universitaire. Des consentements, libres et éclairés, écrits ont été obtenus par tous les participants contrôles et par les représentants légaux des patients incapables de communiquer. Dans les cas où les patients ont récupéré une communication fonctionnelle lors des acquisitions, leur accord oral a également été obtenu.

CHAPITRE 2. PREDIRE LA RECUPERATION INDIVIDUELLE

« La science ne connaît qu'une loi : la contribution scientifique »(Galilée)

Sur base de l'article suivant:

> Gosseries O* & Whyte J* (*co-premiers), Chervoneva I, DiPasquale MC, Giacino J, Kalmar K, Katz D, Novak P, Long D, Childs N, Mercer W, Maurer P, Eifert B. Predictors of short-term outcome in brain-injured patients with disorders of Consciousness. S. Laureys *et al.* (Eds.), *Progress in Brain Research*, 177: 63-72, 2009.

2.1 Introduction

Prédire la récupération fonctionnelle des patients en état de conscience altérée reste toujours difficile à établir au niveau individuel. Cette problématique est pourtant essentielle afin d'évaluer la probabilité des futurs progrès des patients, de déterminer la prise en charge thérapeutique et de fournir des indications aux intervenants lors de leurs prises de décisions. Certains facteurs sont toutefois attribués à un meilleur devenir. Plus la récupération de conscience est rapide, plus les chances d'évolution sont bonnes (Giacino et Kalmar, 1997a; Giacino et Zasler, 1997; Giacino et Whyte, 2005). Le pronostic de récupération des patients diagnostiqués en état de conscience minimale est plus favorable que celui des patients en état d'éveil non-répondant (Noé *et al.*, 2012). Luauté *et al.* (2010) rapportent par exemple que plus d'un tiers des patients en état de conscience minimale évoluent encore un an après l'accident cérébral alors que les patients en état d'éveil non-répondant ne montrent plus d'évolution à ce stade. L'étiologie fournit également une indication pronostique puisque les patients dont l'étiologie est traumatique se rétablissent généralement mieux que ceux dont l'étiologie est non-traumatique (particulièrement les anoxies) (The Multi-Society Task Force on PVS, 1994b). La durée de convalescence est d'environ un an lorsque l'étiologie est traumatique mais se réduit à trois mois dans les cas d'étiologie non-traumatique. De plus, la probabilité de récupération est liée à la sévérité des lésions cérébrales, et dépend de la localisation, de l'étendue, et de la nature des dommages cérébraux. Le jeune âge du patient (Ritchie *et al.*, 2000; Millis *et al.*, 2001; Luauté J *et al.*, 2010) et l'absence d'antécédents médicaux (ex : alcoolisme, abus de drogue, maladie mentale) sont aussi des facteurs favorisant un meilleur pronostic (The Multi-Society Task Force on PVS, 1994a; Laureys *et al.*, 2001). La réapparition d'une poursuite visuelle semble également prédire la récupération progressive d'autres signes de conscience (Giacino et Kalmar, 1997b; Dolce *et al.*, 2011). Enfin, Whyte *et al.* (2005) ont montré que pour les patients d'étiologie traumatique, le score obtenu à la '*Disability Rating Scale*' (DRS, Rappaport *et al.*, 1982) lors de l'admission en centre de réadaptation, le temps écoulé depuis l'accident et la présence de signes de récupération endéans les deux premières semaines d'admission sont des facteurs qui permettent de prédire le score obtenu à la DRS quatre mois après l'accident cérébral ainsi que la réapparition d'une réponse à la commande.

Des méthodes paracliniques, telles que les potentiels évoqués (voir section 3.1), l'IRM ou la TEP ont également montré des vertus prédictives (Owen *et al.*, 2006; Kotchoubey, 2007;

Di *et al.*, 2008). Bien que ces techniques semblent pouvoir identifier un sous-groupe de patients en état d'éveil non-répondant avec un meilleur potentiel de récupération, elles ne sont pas encore employées systématiquement en routine clinique.

L'étude du pronostic des patients en état de conscience altérée est particulièrement difficile à mener aux Etats-Unis en raison d'un service restreint de soins de santé (réadaptation intensive) pour les patients qui présentent peu d'évolution endéans les premières semaines après l'accident cérébral. Cette directive se base sur les croyances qu'une évolution significative est peu probable chez ces patients et que la réadaptation nécessite la participation volontaire des patients. De plus, rien ne montre actuellement que les services de réadaptation intensive améliorent réellement le devenir de ces patients. Ils rentrent alors à domicile avec leurs proches ou sont envoyés dans des maisons de repos non spécialisées peu après leur accident, et par conséquent, ils ne sont pas inclus dans les études réalisées en centres de réadaptation.

La plupart des études de pronostic incluent des patients dès leur accident cérébral. Par conséquent, une large proportion de ces patients vont récupérer une conscience rapidement (c.-à.-d. ceux ayant des lésions cérébrales modérées), et ces facteurs pronostiques ne sont peut-être pas les mêmes que ceux des patients qui restent plus longtemps en état de conscience altérée. D'autres études évaluent des patients sur des intervalles de temps plus longs mais restreignent leur prédiction à une variable dichotomique (récupération de conscience *versus* pas de récupération), et ne prennent donc pas en compte la récupération fonctionnelle globale (ex : Multi-Society Task Force). Dans ce contexte, il est important d'examiner si ces patients en état de conscience altérée lors de leur admission en centre de réadaptation vont récupérer suffisamment lors de cette période afin de montrer un meilleur potentiel de récupération que ce qui est actuellement défini pour cette population. En outre, si les facteurs pronostiques à court terme sont assez précis pour guider la prise en charge individuelle, cela aidera également à améliorer les critères d'admission dans les centres de réadaptation et d'en faire bénéficier les individus avec de bonnes chances de récupération. Dans ce contexte, trois questions se posent : 1) Quel est le taux de récupération chez les patients en état de conscience altérée lors de leur séjour en centre de réadaptation ? 2) Quelles sont les variables disponibles à l'admission qui aideraient à prédire le niveau de récupération lors du séjour hospitalier? 3) Existe-t-il des différences au niveau des facteurs prédictifs pour les patients dont l'étiologie est traumatique *versus* non-traumatique dans cet intervalle de temps ?

2.2 Evaluation pronostique comportementale au stade subaigu

En collaboration avec le Dr John Whyte, nous avons tenté de répondre à ces questions lors de mon séjour au *Moss Rehabilitation Research Institute* à Philadelphie aux Etats-Unis (Whyte & Gosseries *et al.*, 2009). Cet institut accueille des patients qui ont subit des lésions cérébrales et propose des programmes de réadaptation spécifique pour les patients en état d'éveil non-répondant et en état de conscience minimale. Dans ce contexte américain, les critères d'admission en centre de réadaptation sont assez stricts pour ces patients et les séjours y sont plus courts qu'en Belgique. Si les patients ne démontrent aucun progrès considérable après six semaines de revalidation, ils doivent généralement quitter l'établissement. En Belgique, les centres de réadaptation accueillent en général les patients pour une durée de six mois.

Nous nous attendons à observer un rétablissement plus important lors des premières semaines d'admission, avec comme facteurs pronostiques l'étiologie, la durée écoulée depuis l'accident et le niveau fonctionnel à l'admission. Dans cette étude rétrospective, 135 patients (99 cas d'étiologie traumatique) inclut dans les programmes spécialisés de sept centres de réadaptation ont été évalués chaque semaine au moyen de la DRS.

La DRS est une échelle utilisée de manière internationale qui évalue les handicaps des patients sévèrement cérébrolésés afin de suivre leur récupération fonctionnelle du coma jusqu'à leur réinsertion sociale (Rappaport *et al.*, 1982). Cette échelle mesure l'éveil et les réponses comportementales (ouverture des yeux, communication, motricité), les capacités cognitives nécessaires aux activités quotidiennes (alimentation, toilette et orientation), la dépendance aux autres (niveau d'autonomie) et l'adaptation psychosociale (travail en collectivité). Le score total varie de 0 (pas de déficit) à 29 ('état végétatif extrême'). Cette échelle ne différencie pas les patients en état d'éveil non-répondant des patients en état de conscience minimale puisqu'elle a été élaborée avant l'introduction des critères de l'état de conscience minimale (Giacino *et al.*, 2002).

Trois variables à prédire ont été évaluées: le score de la DRS 13 semaines après la lésion cérébrale (DRS_{13}), le taux de changement observé six semaines après l'admission dans le centre de réadaptation (c.-à.-d. la différence entre le score de la DRS à l'admission et le score après six semaines, $Change_{DRS6}$), et pour les patients qui ne répondaient pas à la commande à l'admission, l'intervalle de temps entre la première réponse à la commande et les deux premières semaines d'admission (T_{Follow}) (tableau 3).

	Traumatic brain injury (TBI)			Non-traumatic brain injury (NTBI)			Definition
	No. of subjects	Mean/median/ SD	Min./max.	No. of subjects	Mean/ median/SD	Min./max.	
DRS_{13}	99	18.14/20/5.65	5/28	36	19.72/20.5/4.3	9/26	DRS score at week 13 post-injury
$Change_{DRS6}$	99	4.96/4/4.23	−2/11	36	2.86/2.5/2.93	−1/16	[DRS score at enrollment]–[DRS score 6 weeks later]
T_{Follow}	71	62.04/30/79.72	0/473	37	42.27/27/44.73	0/196	[Date of command following or date of discharge if not following commands]−[date of 2 weeks post-admission]

Tableau 3. Caractéristiques des variables à prédire (Gosseries & Whyte *et al.*, 2009).

Les facteurs prédictifs étaient l'étiologie, le score de la DRS à l'admission dans le centre, l'intervalle de temps entre la lésion cérébrale et l'admission, l'âge, le genre et l'ethnicité (tableau 4). Le taux de changement observé dans les deux premières semaines d'admission a également été inclus comme facteur prédictif pour la variable T_{Follow} afin de satisfaire aux critères statistiques. Les analyses ont été réalisées à l'aide des logiciels Systat et SAS (régression robuste et modèle de Cox). Pour des informations méthodologiques complémentaires, voir Gosseries & Whyte *et al.*, 2009.

	DRS_{13} and 6-week change		T_{Follow}	
	TBI ($N = 99$)	NTBI ($N = 36$)	TBI ($N = 71$)	NTBI ($N = 37$)
Continuous variables	Mean/median/SD	Mean/median/SD	Mean/median/SD	Mean/median/SD
Age	31.58/28/14.09	40.78/39.5/16.33	28.79/26/12.54	36.89/35/14.85
$Log T_{enroll}$	5.55/5.39/0.55	5.44/5.51/0.49	5.59/5.39/0.59	6.05/5.73/1.29
(T_{enroll})	(50.4/42/20.15)	(45.75/45.5/14.18)	(52.37/42/23.07)	(115.49/53/186.19)
DRS_{enroll}	22.85/23/2.23	23.06/23/2.57	23.84/24/2.14	23.84/24/1.72
Nominal variables	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)
Gender				
Male	67 (67)	15 (41.7)	54 (76.06)	13 (64.86)
Female	32 (32.3)	21 (58.3)	17 (23.94)	24 (35.14)
Ethnicity				
White	77 (77.8)	29 (80.5)	61 (85.91)	28 (75.68)
Non-white	22 (22.2)	7 (19.4)	10 (14.09)	9 (24.32)

Abbreviations: $Log T_{enroll}$: $\log_2$ transformation of T_{enroll}; T_{enroll}: date of command following−date of enrollment; DRS_{enroll}: DRS score at enrollment.

Tableau 4. Caractéristiques des variables prédictives (Gosseries & Whyte *et al.*, 2009).

Nos résultats ont montré que pour la variable DRS_{13}, aucune des données démographiques (âge, genre et ethnicité) n'a prédit une récupération. L'intervalle de temps entre la lésion et l'admission ainsi que le score à l'admission étaient par contre de bons facteurs de prédiction ($p<0.0001$) alors que l'effet de l'étiologie n'était pas significatif

(p=0.08). Pour la variable $Change_{DRS6}$, l'étiologie était un facteur prédictif (p=0.01 - deux points de plus à la DRS pour les patients d'origine traumatique). L'intervalle de temps entre l'accident et l'admission était également un bon facteur de récupération (p<0.003), contrairement au score de la DRS à l'admission (p=0.3). Enfin, pour la variable T_{Follow}, seuls le score à la DRS à l'admission et les améliorations observées dans les deux premières semaines après l'admission étaient des facteurs significatifs (p=0.03 et p=0.01 respectivement). En effet, les patients présentant de meilleurs scores à l'admission et ceux qui ont montré des améliorations endéans les deux premières semaines ont récupéré plus rapidement une réponse à la commande que les autres.

La majorité des patients, toute étiologie confondue, ont donc présenté une récupération considérable (spontanée et/ou liée à la prise en charge thérapeutique) lors de leur séjour en centre de rééducation. 84% des patients ont montré une amélioration de leur score à la DRS d'au moins un point durant les six semaines d'observation (85% pour les étiologies traumatiques et 81% pour les non-traumatiques), et 61% des patients qui ne présentaient pas de réponse à la commande à l'admission ont été capables de répondre à la commande avant leur sortie du centre (68% pour les étiologies traumatiques et 50% pour les non-traumatiques). Nos observations confirment que le temps écoulé entre la lésion cérébrale et l'admission est un facteur clé de récupération, le temps réduisant les chances de récupération (pour les variables DRS_{13} et $Change_{DRS6}$). Le score de la DRS à l'admission prédit le score obtenu 13 semaines après la lésion cérébrale (*DRS13*) mais ne prédit pas le taux de récupération endéans les six semaines d'hospitalisation ($Change_{DRS6}$). Ces résultats suggèrent que le score à l'admission est un facteur qui prédit le statut fonctionnel plutôt que le changement fonctionnel, alors que la durée écoulée entre l'admission et la lésion cérébrale est particulièrement pertinente pour la probabilité de changement. Le score de la DRS à l'admission était aussi prédictif du temps écoulé jusqu'à la première réponse à la commande. Ceci indique que, à un taux de changement équivalent, les patients qui présentent un meilleur niveau fonctionnel ont besoin de moins d'amélioration, et donc moins de temps, pour atteindre les critères de réponse à la commande. L'effet de l'étiologie est plus complexe. Les patients d'origine non-traumatique ont montré de moins bons taux de changement dans les six semaines d'hospitalisation que les patients d'origine traumatique (tendance également observée pour la variable DRS_{13}). Cependant, l'étiologie ne prédit pas le temps nécessaire aux patients pour récupérer la capacité de répondre à des commandes simples. Ce dernier effet peut être dû au fait que nous avons inclus dans les analyses le taux de changement endéans les

deux premières semaines, ce qui peut réduire l'effet de variables moins directes comme le temps écoulé depuis la lésion cérébrale ou l'étiologie. Même si les patients d'étiologie non-traumatique ont présenté une moins bonne récupération dépendamment du facteur choisi, la prédiction que le pronostic des patients d'étiologie non-traumatique déclinerait beaucoup plus vite avec le temps n'a pas été retrouvée ici. Ce résultat est en contradiction avec les études précédentes qui montrent une fenêtre de récupération plus courte pour les patients dont l'origine est non-traumatique (The Multi-Society Task Force on PVS, 1994a; Bruno *et al.*, 2010a). Notons cependant que l'impact du temps est probablement plus important dans les trois à douze mois après l'accident alors que les données présentées ici ne concernent que les premières semaines après la lésion cérébrale.

Cette étude a quelques limites. Premièrement, elle est basée sur un échantillon sélectionné au préalable et non sur la population générale de patients sévèrement cérébrolésés. Les patients qui ont récupéré dans les heures ou les jours suivant leur coma n'ont donc pas été inclus dans l'étude. De plus, il existe également un biais de sélection d'admission dans les centres de réadaptation. Comme les cliniciens connaissent souvent le pronostic plus réservé des patients d'origine non-traumatique, ils peuvent être plus enclins à refuser ces patients (ce biais a pu interférer avec nos résultats concernant l'étiologie). Il n'y a cependant pas d'évidence directe de critères d'admission plus stricts pour les étiologies non-traumatiques puisque les scores à l'admission étaient légèrement moins bons pour les étiologies autres que traumatiques. Deuxièmement, la durée relativement courte de cette étude, due à la réalité actuelle des séjours en centres de rééducation aux Etats-Unis, implique qu'un certain nombre de patients n'ont pas répondu à la commande lors de leur sortie du centre et ont donc été censurés lors de l'analyse statistique. Des intervalles plus longs et un échantillon plus grand auraient permis de définir plus clairement les facteurs de récupération.

2.3 Conclusion

Dans notre échantillon de patients en état de conscience altérée admis en centre de réadaptation, une récupération significative a été observée lors du séjour hospitalier. En effet, la plupart des patients ont présenté des améliorations aux scores de la DRS. Aussi, pour la majorité des patients ne démontrant pas de compréhension verbale à l'admission, la réapparition d'une réponse à la commande a été observée. L'intervalle de temps entre la lésion cérébrale et l'admission ainsi que le score de la DRS à l'admission étaient prédictifs de deux des trois variables à prédire. L'étiologie était prédictive du taux d'amélioration observé

endéans les six semaines d'hospitalisation, alors que ce n'était pas le cas pour le score de la DRS à 13 semaines, ni pour le moment de la première réponse à la commande. Le taux de changement dans les deux premières semaines d'admission était par contre largement prédictif d'une récupération d'une réponse à la commande, suggérant que la trajectoire clinique en elle-même est hautement prédictive. Aucun des modèles de prédiction ne peut cependant être utilisé dans le cadre des décisions cliniques individuelles en raison d'une trop grande variabilité entre les patients. Enfin, l'échelle DRS étant une échelle qui permet de suivre les patients jusqu'à leur réinsertion sociale, elle n'est probablement pas la plus sensible pour détecter de fines améliorations chez les patients en état de conscience altérée. Il serait judicieux de réaliser une étude similaire au moyen de la CRS-R (Giacino *et al.*, 2004). Une étude utilisant cette dernière échelle est d'ailleurs parue très récemment et a montré que sur 36 patients admis en centres de réadaptation en Espagne, huit patients (22%) avaient émergé de l'état de conscience minimale un an après l'accident. Parmi ceux-ci, sept étaient en état de conscience minimale et seulement un en état d'éveil non-répondant à l'admission. En plus du diagnostic à l'admission, la durée écoulée depuis l'accident cérébral et la présence de signes de conscience en plus de la poursuite visuelle ont été rapportées comme de bons facteurs pronostiques (Noé *et al.*, 2012).

CHAPITRE 3. MESURES ELECTROENCEPHALOGRAPHIQUES COMME OUTIL DIAGNOSTIQUE ET PRONOSTIQUE

« Parce que la science nous balance sa science, science sans conscience égale science de l'inconscience » (MC Solaar)

Sur base des articles suivants:

Gosseries O* & Lehembre R* (*co-premiers), Lugo Z, Jedidi Z, Chatelle C, Sadzot B, Laureys S, Noirhomme Q. Electrophysiological investigations of brain function in coma, vegetative and minimally conscious patients. *Archives Italiennes de Biologie*, sous presse, 2012.

Gosseries O* & Schnakers C* (*co-premières), Ledoux D, Vanhaudenhuyse A, Bruno MA, Demertzi A, Noirhomme Q, Lehembre R, Damas P, Goldman S, Peeters E, Moonen G, Laureys S. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. *Functional Neurology*, 26(1): 25-30, 2011.

Boly M, Garrido MA, Gosseries O, Bruno MA, Boveroux P, Schnakers C, Massimini M, Litvak V, Laureys S, Friston KJ. Preserved feedforward but impaired top-down processes in the vegetative state. *Science*, 332(6031): 858-62, 2011 & Response to comment. *Science*, 334(6060): 1203, 2011.

3.1 Introduction

Nous avons vu dans l'introduction générale que les premiers résultats concernant les patients en état de conscience altérée provenaient des études réalisées par IRM et TEP. Ces deux techniques d'imagerie coûtent chères et sont très incommodantes puisqu'elles nécessitent le déplacement des patients qui se trouvent bien souvent dans des états critiques. L'EEG et ses paramètres dérivés sont en revanche des techniques transportables qui peuvent être utilisées au chevet des patients et de moindre coût. L'EEG permet d'enregistrer l'activité électrique cérébrale en continu en fixant des électrodes sur le scalp. Le signal EEG correspond à la somme des activités neuronales, essentiellement post-synaptiques, représentées sur un axe temporel.

Il existe quatre approches principales basées sur l'EEG qui peuvent contribuer à l'évaluation des patients sévèrement cérébrolésés : l'inspection visuelle de l'EEG, l'EEG quantitative, les potentiels évoqués et l'interface cerveau-ordinateur (Gosseries & Lehembre *et al.*, sous presse). Premièrement, l'EEG clinique standard est un examen de routine dans les unités neurologiques qui donne une vision globale de l'électrogenèse spontanée d'un patient et peut, par exemple, mettre en évidence une activité épileptiforme anormale ou une lésion cérébrale asymétrique. Un effet visible sur l'EEG est un ralentissement de l'activité cérébrale proportionnel à la gravité des lésions cérébrales. En raison de son aspect hétérogène et variable, cet examen n'a guère de valeur diagnostique chez les patients en état de conscience altérée (Kulkarni *et al.*, 2007). Il peut néanmoins servir à confirmer la mort cérébrale (Fischer, 1997) et présente une pertinence diagnostique dans les cas de patients en locked-in syndrome complet (Schnakers *et al.*, 2009a). Le tracé EEG a surtout un plus grand intérêt pronostique. Dans les cas de coma alpha/thêta non réactif ou de tracés paroxystiques, le pronostic est défavorable (Kaplan *et al.*, 1999; Berkhoff *et al.*, 2000; Niedermeyer et Da Silva, 2005). Par contre, lorsque l'EEG réagit aux stimulations ou présente des tracés variables, comme des cycles de sommeil, le pronostic est souvent meilleur (Valente *et al.*, 2002; Thenayan *et al.*, 2010). Plus récemment, notre groupe a d'ailleurs montré que les patients en état de conscience minimale présentent des épisodes de sommeil paradoxal et des cycles d'ondes lentes similaires aux sujets sains, alors que les patients en état d'éveil non-répondant ne semblent pas présenter ces caractéristiques typiques de sommeil (Landsness & Bruno *et al.*, 2011).

La deuxième approche est l'analyse quantitative de l'EEG, qui fournit des mesures objectives variées de l'activité cérébrale grâce à un traitement des données EEG. Ces analyses permettent de repérer des caractéristiques non visibles sur les tracés bruts. Il est possible, par

exemple, de calculer la densité spectrale de puissance (León-Carrión *et al.*, 2008), la complexité du signal, comme l'entropie (Gosseries *et al.*, 2011b; Wu *et al.*, 2011b), ou le niveau de connectivité entre différentes régions du cerveau. Les analyses de connectivité peuvent se réaliser au moyen de mesures de synchronisation, de cohérence ou d'information mutuelle (Nunez *et al.*, 1997; Nunez *et al.*, 1999; Pereda *et al.*, 2005). En outre, l'EEG quantitative inclut aussi des méthodes de reconstruction de source qui permettent de reconstituer l'activité cérébrale sous-jacente à partir des électrodes de surface (Michel *et al.*, 2004), et donc de localiser une activité spécifique dans le cerveau. De récentes études ont mis en évidence des différences diagnostiques et pronostiques entre les patients en état d'éveil non-répondant et les patients en état de conscience minimale (Schnakers *et al.*, 2008a; Babiloni *et al.*, 2009; Lehembre & Bruno *et al.*, sous presse). Il n'est cependant pas encore possible d'identifier un paramètre susceptible de produire un diagnostic correct au niveau individuel.

La troisième approche baptisée potentiels évoqués (PE) se fonde sur la moyenne des réponses produites par un stimulus et reflète le traitement de l'information dans le temps, allant des structures réceptrices de bas niveau vers les cortex associatifs supérieurs (Luck, 2005). On distingue deux catégories : les PE de courte latence qui sont obtenus dans un laps de temps situé entre 0 et 100 ms après la présentation d'un stimulus (par ex. les potentiels évoqués auditifs du tronc cérébral ou les potentiels évoqués somatosensoriels), et les PE cognitifs de longue latence qui sont obtenus après 100 ms (par ex. la composante P3 ou la négativité de discordance – MMN). Les PE de courte latence ou composantes exogènes sont obtenus par des stimulations externes visant à évaluer les voies auditives, visuelles ou somatosensorielles. L'absence de ces PE chez les patients en état de conscience altérée est associée à un mauvais pronostic mais leur présence n'est pas nécessairement le signe d'une bonne récupération (Fischer *et al.*, 2001; Amantini *et al.*, 2005; Laureys *et al.*, 2005b). Les composantes endogènes ou PE cognitifs permettent quant à eux d'évaluer les fonctions cognitives résiduelles au moyen de paradigmes passifs et l'état de conscience au moyen de paradigmes actifs (voir tableau 5). La présence de différentes composantes, comme les N1, MMN, P3, N400 et P600, paraît constituer un bon marqueur pronostique d'une issue favorable, mais ces composantes ne peuvent actuellement être utilisées pour établir un diagnostic différentiel individuel entre les patients en état de conscience minimale et les patients inconscients (Kotchoubey, 2005; Daltrozzo *et al.*, 2007; Fischer *et al.*, 2010; Höller *et al.*, 2011). Le tableau 5 résume les études de potentiels évoqués chez les patients en état de

conscience altérée. Parallèlement à l'utilisation de paradigmes passifs, des chercheurs ont également mis au point des paradigmes actifs basés sur une réponse à la commande (ex : serrer la main, compter l'occurrence de son prénom à l'écoute d'une liste de prénoms), similaires à ceux utilisés en IRMf pour évaluer l'état de conscience. Ils ont démontré que l'amplitude d'une composante électrique peut être modulée quand le sujet se concentre sur une tâche durant la présentation du stimulus (Schnakers *et al.*, 2008d; Cruse *et al.*, 2011; Faugeras *et al.*, 2011; Fellinger *et al.*, 2011), ce qui constitue une preuve de conscience (tableau 5). L'absence de réponse n'est toutefois pas une preuve d'absence de conscience puisqu'une aphasie ou un manque de collaboration du patient peuvent entraîner des faux négatifs.

Enfin, la dernière approche comprend les interfaces cerveau-ordinateur. Dès lors que des signes de conscience ont été observés chez un patient gravement cérébrolésé, les interfaces cerveau-ordinateur constituent un moyen de communication potentiel pour les patients en état de conscience minimale, sans faire intervenir les nerfs périphériques et les muscles. Ces interfaces convertissent directement l'activité cérébrale en signaux de contrôle pour des équipements électroniques (Wolpaw, 2010). Ces techniques se sont beaucoup perfectionnées au cours des deux dernières décennies (Kubler et Neumann, 2005; Halder *et al.*, 2010) mais elles ne sont toutefois pas facilement adaptables aux patients récupérant du coma en raison des déficiences visuelles, auditives ou cognitives, et à cause des différentes lésions cérébrales qui affectent le signal EEG. Des recherches sont encore nécessaires avant qu'elles puissent être utilisées en routine clinique.

Dans la suite de ce chapitre, nous allons étudier l'intérêt diagnostique et pronostique d'une mesure quantitative, l'EEG-entropie (Gosseries *et al.*, 2011b), et d'une mesure de potentiels évoqués auditifs couplée à une analyse spécifique de reconstruction de source (Boly *et al.*, 2011a).

	References	Etiology	Interval	N	Diagnostic	Main findings
Passive paradigm						
N1	Glass et al. 1998	TBI	< 3 m	8	VS/UWS	N1 in 87% of VS/UWS with longer latency. No prognostic value for recovery.
	Guérit et al. 1999	TBI/NTBI	< 6 m	103	comatose (GCS ≤ 10)	N1 occurrence, latency and amplitude related with GCS. Presence of N1 is good prognosis but no prognostic value if absence of N1.
	Lew et al. 2003	TBI	< 1 w	22	comatose (GCS ≤ 8)	Prognostic value: N1 associated with favorable outcome.
	Fischer et al. 2004	TBI/NTBI	< 3 m	346	comatose	Presence of N1 gives a probability of awakening up to 87%.
MMN	Kane et al. 1996	TBI	< 1 m	54	comatose (GCS ≤ 8)	Very good predictor of recovery. Presence of MMN predicted return of consciousness and preceded changes in GCS.
	Kotchoubey et al. 2003	TBI/NTBI	na	79	VS/UWS, (E)MCS	MMN in 65% of VS/UWS and 34% of MCS. Complex (musical) tones elicit MMN more frequently and of a larger amplitude than pure tones.
	Fischer et al. 2004	TBI/NTBI	< 2 m	346	comatose	Prognostic value for recovery. When MMN present, 89% of patients awakened. No patient with MMN became permanently VS/UWS.
	Kotchoubey et al. 2005	TBI/NTBI	1 - 127 m	98	VS/UWS, (E)MCS	Presence of MMN related to a better outcome. No difference between VS/UWS and MCS.
	Naccache et al. 2005		< 3 m	30	comatose (GCS ≤ 8)	Good predictor of awakening : MMN predicted awakening with a specificity of 93%, a sensitivity of 56%, and with a positive predictive value of 90%.
	Fischer et al. 2006	NTBI	< 2 w	62	comatose (GCS ≤ 8)	Prognostic value with very high probability awakening when MMN present and nonawakening when MMN are absent.
	Wijnen et al. 2007	TBI/NTBI	< 5 m	10	VS/UWS	MMN-amplitude and latency predicted the patients' outcome on recovery to consciousness.
	Qin et al. 2008	TBI/NTBI	< 6 m	12	coma, VS/UWS, MCS	Presence of MMN correlated with recovery of consciousness. Subject's own name is effective in evoking. MMN and has potential prognostic values in predicting recovery of consciousness.
	Fischer et al. 2010	TBI/NTBI	4 - 261 m	27	VS/UWS, MCS	Presence of MMN 19%. No difference between VS/UWS and MCS.
P3	Yingling et al. 1990	TBI/NTBI	< 1 m	8	comatose (GCS ≤ 10)	Presence of P3 is related to a good prognosis in the acute stage.
	Gott et al. 1991	NTBI	< 1m	20	coma	Presence of P3 (30%) associated with awakening (83%), but absence of a P3 did not preclude it. Presence of a P3 correlated with higher GCS.
	Signorino et al. 1997	TBI	< 1 w	25	comatose (GCS ≤ 9)	Prediction of outcome. Emotional stimulations increase number of responders (36% to 52%). No P3 in 40% with 50% of them died.
	Glass et al. 1998	TBI	< 3 m	8	VS/UWS	Presence of P3 is compatible with a higher probability for improvement but nondetection does not indicate bad prognosis. Presence of P3 in 38% with 67% regained consciousness (vs none of the non-responders).
	Guérit et al. 1999	TBI/NTBI	< 6 m	103	comatose (GCS ≤ 10)	Occurrence, latencies and amplitudes related with the GCS. Presence of P3 is good prognosis but no prognostic value if absence of P3.
	Lew et al 2003	TBI	< 1 w	22	comatose (GCS ≤ 8)	Presence of P3 can predict a return of consciousness. P3 associated with good clinical outcomes.
	Kotchoubey 2005	TBI/NTBI	1-127 m	98	VS/UWS, (E)MCS	No difference between VS/UWS and MCS.
	Perrin et al. 2006	TBI/NTBI	2 w - 10 m	15	VS/UWS, MCS, LIS	No difference between VS/UWS and MCS. Patient's own name more likely to generate a P3 than a simple sound. P3 observed in all LIS and MCS and in 3 of 5 VS/UWS. Delayed P3 latency for MCS and VS/UWS patients. Partial preservation of semantic processing in DOC patients.
	Fischer et al. 2008	TBI/NTBI	< 3 m	50	comatose (GCS ≤ 8)	Presence of P3 (42%) highly correlated with awakening. P3 increases prognostic value of MMN alone.
	Cavinato et al. 2009	TBI	2 - 3 m	34	VS/UWS	P3 correlated with recovery of consciousness. P3 highly predictive of recovery of consciousness.
	Fischer et al. 2010	TBI/NTBI	4 - 261 m	27	VS/UWS, MCS	No difference between VS/UWS and MCS. P3 in 26%.
N400	Schoenle and Witzke 2004	TBI/NTBI	na	120	VS, (E)MCS	Presence of N400 in some VS and in a majority of (E)MCS. Semantic processes can be relatively preserved in DOC.
	Kotchoubey et al. 2009	TBI/NTBI	2 - 108 m	30	VS/UWS, MCS, LIS	Recognition of affective prosody in 22%. Residual detection of affective mismatch due to violations of emotional context of stimulation in DOC.
Active paradigm						
P3	Schnakers et al. 2008	TBI/NTBI	1 - 288 m	22	VS/UWS, MCS	Increase of the P3 in some MCS patients in active compared to passive condition. No difference in VS/UWS.
	Schnakers et al. 2009	NTBI	1 m	1	LIS	Increase of the P3 in active compared to passive condition.
P3& MMN	Bekinschtein et al., 2009	TBI/NTBI	1 w - 6 m	8	VS/UWS, MCS	3 out of 4 MCS presented a global effect and only a local effect was observed in VS/UWS. Evidence of conscious processing.

Note. MMN = mismatch negativity; N= Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; EMCS = emergence of MCS; LIS = locked in syndrome; TBI=traumatic brain injury; NTBI=non traumatic brain injury; w = weeks; m = months; GCS = Glasgow Coma Scale

Tableau 5. Principales études de potentiels évoqués chez les patients en état de conscience altérée en condition passive et active. La composante N1 se produit en réponse à une stimulation auditive, la négativité de discordance (MMN) et la P3 répondent à un stimulus déviant et nouveau, et les composantes N400 et P600 répondent à un changement sémantique (Gosseries & Lehembre *et al.*, sous presse).

3.2 EEG-entropie

Étant donné que l'interprétation du signal brut de l'EEG requiert une expertise considérable et une formation spécialisée, des mesures plus simples et plus standardisées des fonctions cérébrales sont souhaitables, notamment pour quantifier le niveau de conscience des patients en état de conscience altérée (Young, 2000). Des études précédentes recourant à la quantification automatisée de l'EEG ont mis en évidence une corrélation entre l'indice bispectral de l'EEG et l'évaluation clinique de la conscience (Gilbert *et al.*, 2001; Gill *et al.*, 2003; Schnakers *et al.*, 2005). Le moniteur bispectral est un outil commercial qui sert principalement à surveiller le degré de sédation durant l'anesthésie (Glass *et al.*, 1997; Aspect Medical Systems, 2000). L'inconvénient de cet outil est qu'il emploie des algorithmes mathématiques non publiés, ce qui en fait une « boîte noire », peu appréciée des électrophysiologistes et des neurologues. Dans cette étude, nous avons donc concentré notre attention sur une autre mesure, l'EEG-entropie, pour évaluer le niveau de conscience des patients gravement cérébrolésés. Issue de la thermodynamique, l'entropie est une mesure de désordre qui décrit l'irrégularité, la complexité ou l'imprévisibilité d'un signal EEG (Palanca *et al.*, 2009). Un signal EEG régulier, comme celui enregistré en cas de sommeil lent ou d'anesthésie profonde, a une entropie très basse, alors que la multitude d'activités cérébrales chez un sujet conscient produit un signal plus complexe (entropie élevée). Nous avons ici utilisé un dispositif en ligne automatisé de mesure de l'*entropie spectrale équilibrée par le temps et la fréquence* (*time-frequency balanced spectral entropy*, Datex-Ohmeda S/5, Helsinki – pour plus d'informations sur les méthodes, voir Gosseries *et al.*, 2011b). Ce monitoring a été validé précédemment pour surveiller le niveau d'anesthésie générale chez les patients au cours d'une intervention chirurgicale (Vakkuri *et al.*, 2004; Hans *et al.*, 2005; Paolo Martorano *et al.*, 2006).

Dans le cadre de cette étude multicentrique, nous avons suivi 56 patients en état de conscience altérée (âgés de 54±19 ans, 37 hommes, 23 cas d'étiologie traumatique) dont 6 était en comas, 24 en syndrome d'éveil non-répondant et 26 en état de conscience minimale, ainsi que 16 participants sains appariés en âge (50±17 ans, 9 hommes). Les patients ont été évalués dans les stades aigu (≤1 mois après la lésion, n=29) ou chronique (>1 mois après la lésion, n=27) (tableau 6). Tous les patients ont été évalués de manière répétée au moyen de la CRS-R (Giacino *et al.*, 2004; Schnakers *et al.*, 2008b).

Diagnostic \ Stade	Aigu		Chronique		Total
	N	CRS-R	N	CRS-R	
Coma	6	1±1	0	/	6
Syndrome d'éveil non-répondant	14	4±1	10	5±1	24
Etat de conscience minimale	9	11±3	17	11±4	26
Sujet sain	/	/	/	/	16
Total	29		27		72

Tableau 6. Nombre de participants et scores totaux à l'échelle de récupération du coma (CRS-R) en fonction du diagnostic et du stade chez les patients.

L'activité électrique cérébrale au repos a été enregistrée pendant 10 minutes au moyen d'un capteur placé sur le front et la tempe. Le moniteur enregistrait automatiquement deux types d'entropie : l'entropie d'état (EEG corticale uniquement) et l'entropie de réponse (incluant aussi un électromyogramme frontal) (Viertiö-Oja *et al.*, 2004). Les valeurs de l'entropie d'état sont celles rapportées ici et elles peuvent varier de 0 (suppression de l'EEG) à 91 (état d'éveil). Les analyses statistiques ont été exécutées au moyen du logiciel STATA (Version 11. College Station, TX : StataCorp LP 2009) en incluant un test de Spearman, des tests de Mann-Whitney et de Kruskal-Wallis, un modèle de régression logistique ainsi qu'une analyse de la caractéristique de fonctionnement du récepteur (ROC). Les résultats ont été considérés significatifs à $p<0.05$.

Chez les 56 patients, les mesures moyennes de l'EEG-entropie au repos ont montré une corrélation linéaire positive avec les scores CRS-R totaux ($r=0.49$; $p<0.001$) (figure 2). Ce résultat confirme des données préliminaires montrant une corrélation entre l'*entropie approximative* de l'EEG (calculée hors ligne) et l'échelle de coma de Glasgow chez des patients comateux (Lin *et al.*, 2005).

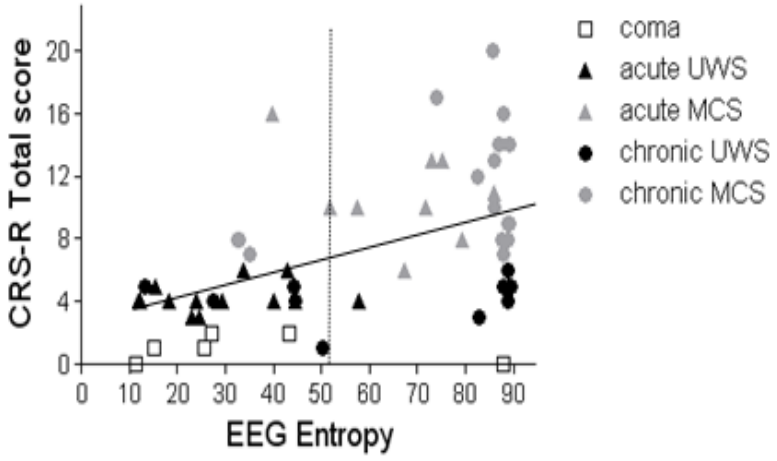


Figure 2. Corrélation entre les valeurs d'EEG-entropie et l'échelle de récupération du coma (CRS-R) selon le diagnostic des patients (UWS: syndrome d'éveil non-répondant, MCS: état de conscience minimale) et le stade (aigu ou chronique). La ligne verticale montre le seuil de différenciation (52) entre patients inconscients et conscients. Noter que les faux positifs sont principalement présents dans les cas chroniques (Gosseries & Schnakers et al, 2011).

Les valeurs moyennes de l'EEG-entropie différaient entre les groupes (35±28 dans le coma ; 45±28 en syndrome d'éveil non-répondant, 73±19 en état de conscience minimale et 89±1 pour les contrôles sains; $p<0.001$), avec des valeurs significativement plus élevées pour les patients en état de conscience minimale que pour les patients en état d'éveil non-répondant ($p=0.003$). Par rapport aux sujets sains, les valeurs d'EEG-entropie étaient donc inférieures de 49% chez les patients en état d'éveil non-répondant et de 18% chez les patients en état de conscience minimale, ce qui indique que la complexité des diverses oscillations cérébrales varie selon le niveau de conscience. Ces résultats corroborent des études antérieures qui montrent que les valeurs bispectrales de patients en état d'éveil non-répondant et en état de conscience minimale étaient respectivement inférieures de 30% et 11% à celles de patients cérébrolésés conscients (Schnakers *et al.*, 2005; 2008a). Des résultats similaires ont également été obtenus dans le cadre de deux études récentes utilisant des mesures d'entropie. La première montre une diminution de 33% de l'*entropie approximative* chez des patients en état d'éveil non-répondant par rapport à des sujets sains (Sarà et Pistoia, 2010). La seconde étude rapporte une diminution de 27% de l*'entropie croisée approximative* chez des patients en état d'éveil non-répondant et une diminution de 8% chez des patients en état de conscience minimale par rapport à des patients cérébrolésés conscients (Wu *et al.*, 2011a). Cette dernière étude ne laissait pas apparaître de différence de groupe entre les patients en syndrome d'éveil non-répondant et ceux en état de conscience minimale.

Nos résultats ont également montré que les valeurs de l'EEG-entropie différaient selon le stade aigu ou chronique (43±24 contre 73±25 respectivement ; $p<0.001$) avec une différence nettement plus importante entre les patients en état d'éveil non-répondant et les patients en état de conscience minimale dans le stade aigu (figure 3).

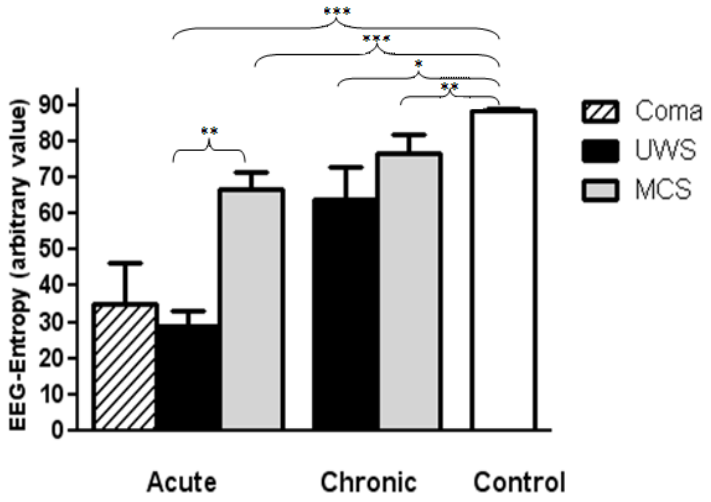


Figure 3. Valeurs d'EEG-entropie chez les patients en stade aigu et chronique selon le diagnostic (coma, syndrome d'éveil non-répondant - UWS, état de conscience minimale - MCS) et chez des sujets contrôles (*p<0.05; **p<0.001; ***p<0.0001) (Gosseries & Schnakers et al, 2011).

De plus, un seuil d'EEG-entropie de 52 a permis de distinguer les patients inconscients (coma et syndrome d'éveil non-répondant) des patients conscients (état de conscience minimale) au stade aigu avec une sensibilité de 89 % et une spécificité de 90 % (figure 2). Ces valeurs étaient meilleures que celles rapportées précédemment utilisant des mesures d'indice bispectral chez des patients en état d'éveil non-répondant et en état de conscience minimale évalués dans les 11 semaines suivant la lésion cérébrale (sensibilité et spécificité de 75 %) (Schnakers *et al.*, 2008a). La mesure de l'EEG-entropie, calculée en ligne, semble donc constituer un outil étonnamment fiable qui pourrait contribuer au diagnostic clinique au stade aigu. Chez les patients chroniques, la sensibilité et la spécificité étaient par contre trop faibles pour tirer des conclusions. En effet, les patients en état d'éveil non-répondant ne présentaient pas de différence significative d'entropie par rapport aux patients en état de conscience minimale au stade chronique. Cette observation peut refléter un processus de réorganisation cérébrale dans le temps (Navarro, 2009) ou elle pourrait être liée à des artefacts musculaires dus à l'augmentation de la spasticité avec le temps. L'importance de la contamination des artefacts musculaires à haute fréquence dans le calcul de l'entropie que nous avons employé ressort clairement dans la figure 4. Un blocage neuromusculaire a instantanément réduit les valeurs d'entropie chez un patient en coma post-anoxique. Ce résultat confirme des études précédentes qui montrent des valeurs bispectrales et d'EEG-entropie non nulles en raison d'artefacts musculaires chez des patients diagnostiqués en mort cérébrale (Vivien *et al.*, 2007; Wennervirta *et al.*, 2007).

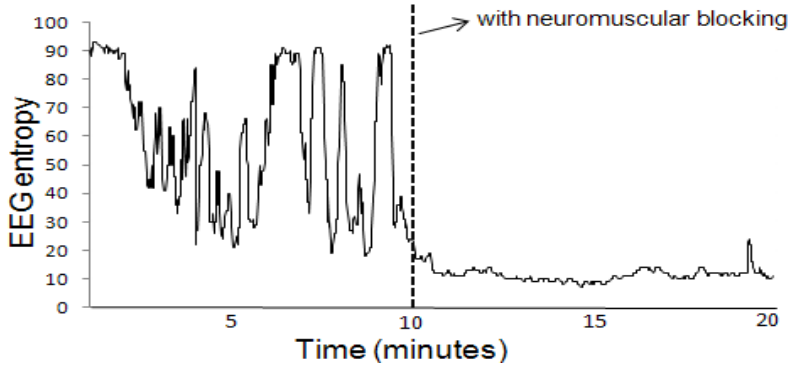


Figure 4. Illustration d'un artefact musculaire dans le calcul de l'EEG-entropie. Un agent neuromusculaire bloquant réduit les valeurs d'EEG-entropie dans un cas d'encéphalopathie post-anoxique (Gosseries & Schnakers et al, 2011).

Nous n'avons pas constaté des valeurs d'EEG-entropie différentes en fonction de l'étiologie (traumatique : 61±28, non-traumatique : 54±28 ; p=0.4), ce qui suggère que la technique peut être appliquée chez tous les patients cérébrolésés. Enfin, nous avons relevé qu'après un an, sur les 56 patients étudiés, 24 étaient décédés, 5 étaient encore en état d'éveil non-répondant, 17 présentaient un handicap grave, 3 présentaient un handicap modéré et 4 avaient repris une vie autonome (données manquantes pour 3 patients). À la différence d'études antérieures qui démontraient l'intérêt pronostique de l'indice bispectral au niveau du groupe (Schnakers *et al.*, 2008a), nous n'avons pas pu mettre en évidence une quelconque différence dans les valeurs d'entropie entre les patients présentant une issue favorable (c.-à-d. une récupération d'une communication fonctionnelle) et une issue défavorable (57±29 contre 57±25 respectivement; p=0.72).

Une limite de l'étude doit être soulignée. Le diagnostic des patients a été réalisé au moyen de la CRS-R et il se peut que certains patients aient été erronément diagnostiqués malgré des évaluations soignées (Laureys et Schiff, 2011). Étant donné que le diagnostic clinique n'est pas certain à 100 %, le taux de 10 % d'erreur que nous avons relevé dans la différenciation entre les patients conscients et les patients inconscients peut refléter des artefacts dans le calcul de l'EEG-entropie (comme l'illustre la figure 4) mais peut également être dû à l'évaluation comportementale elle-même (Schnakers *et al.*, 2009b). Il est dès lors préférable de parler en termes d'index de concordance plutôt que de spécificité et de sensibilité. Ce biais est applicable à presque toutes les études mentionnées dans ce travail. Afin de diminuer ce risque, nous avons néanmoins pris soin de n'inclure que des patients présentant un diagnostic clinique clair.

En résumé, nous avons montré ici une diminution de la complexité des réseaux neuronaux, telle qu'elle apparaît dans les mesures de l'EEG-entropie chez les patients sévèrement cérébrolésés. Des mesures de l'EEG-entropie indépendantes de l'utilisateur nous ont permis de distinguer les patients inconscients des patients en état de conscience minimale au stade aigu avec un index de concordance supérieur à ceux rapportés précédemment pour les mesures bispectrales (Schnakers *et al.*, 2005). Le monitoring en ligne de l'EEG-entropie, aisément utilisable au chevet des patients, peut donc constituer une méthode supplémentaire pour aider les cliniciens dans le diagnostic différentiel de patients non sédatés récupérant du coma. Les paradigmes de calcul automatisé de l'entropie employés devraient cependant être améliorés afin de réduire les artefacts, comme ceux imputables à la spasticité musculaire. D'autres travaux devraient aussi être menés afin de vérifier le potentiel pronostique de la technique. Les résultats obtenus avec l'entropie spectrale sont donc prometteurs mais ne sont pas encore suffisants pour être systématiquement utilisés au niveau individuel dans la routine clinique. C'est pourquoi nous avons approfondi nos recherches avec un autre système fournissant davantage d'informations spatiales et temporelles.

3.3 Potentiels évoqués auditifs

La perception consciente de stimuli externes requiert, comme nous l'avons vu, l'activation de cortex de bas niveau spécialisés mais surtout celle des cortex fronto-pariétaux (Rees *et al.*, 2002; Boly *et al.*, 2004; Dehaene *et al.*, 2006). Toutefois, l'activation des cortex fronto-pariétaux peut également être observée durant le traitement de stimuli subliminaux (Diaz et McCarthy, 2007; Luo *et al.*, 2009). D'autres études réalisées en EEG ont relevé l'importance des composantes de longue latence et d'une connectivité rétrograde impliquant les cortex fronto-pariétaux dans la perception consciente chez des sujets sains (Fitzgerald *et al.*, 2001; Del Cul *et al.*, 2007). Des recherches ont en outre mis en évidence le rôle privilégié de la connectivité rétrograde dans la production des composantes de longue latence (Garrido *et al.*, 2007). Cela donne à penser que le niveau de conscience peut dépendre de l'intégrité de la connectivité rétrograde (ou descendante, c.-à-d. allant des cortex antérieurs vers les cortex postérieurs). Dans la présente étude, nous avons testé cette hypothèse dans le but de découvrir un nouveau biomarqueur potentiel du niveau de conscience chez les patients sévèrement cérébrolésés. Nous avons mesuré les réponses cérébrales induites par des stimulations auditives au moyen des potentiels évoqués (PE) et d'un outil d'analyse complexe, la modélisation causale dynamique (*Dynamic Causal Modeling* – DCM), qui permet de

quantifier la connectivité cérébrale dans les connexions antérogrades et rétrogrades (Friston *et al.*, 2003; David *et al.*, 2006).

Nous avons évalué 21 patients cérébrolésés (8 patients en syndrome d'éveil non-répondant et 13 en état de conscience minimale ; âgés de 48±20 ans, 12 hommes et 7 cas d'étiologie traumatique) et 22 contrôles sains (âgés de 37±19 ans, 7 hommes). Les évaluations comportementales du niveau de conscience ont été effectuées au moyen de la CRS-R. En utilisant un EEG à 60 électrodes (Nexstim Ltd, Helsinki - Virtanen *et al.*, 1999), nous avons enregistré des PE pendant 15 minutes lors d'un paradigme auditif de détection de déviance (Garrido *et al.*, 2008; 2009). Dans chaque série de stimuli, toutes les tonalités étaient d'une seule fréquence et étaient suivies d'une série d'une fréquence différente (figure 5A). La première tonalité d'une série était un déviant, qui devenait finalement un standard après quelques répétitions, de sorte que les stimuli déviants et standards aient les mêmes propriétés physiques. Environ 200 stimuli standards (11^{e} tonalité) et 250 stimuli déviants (1re tonalité) ont été moyennés pour l'analyse du traitement différentiel des sons. Le prétraitement et l'analyse des données ont été réalisés avec SPM8 et SPSS16 (voir Boly et al, 2011a,b pour les détails méthodologiques). Les résultats ont été considérés significatifs à $p<0.05$ et corrigés pour comparaisons multiples.

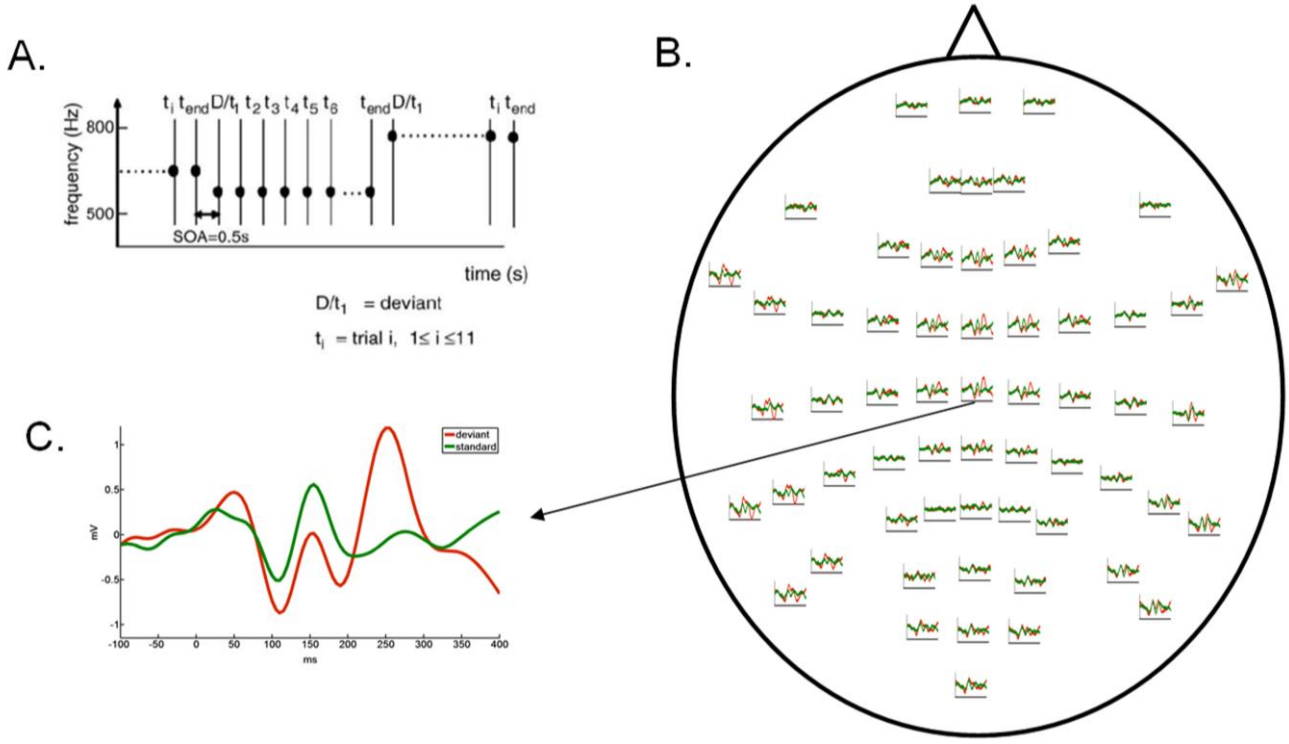


Figure 5. Design et réponses des potentiels évoqués auditifs lors d'un paradigme de détection de déviance. A. La conception expérimentale utilise un stimulus auditif standard qui change sporadiquement de fréquence. La première présentation d'un son est le déviant (D=t1) qui devient standard au travers des répétitions (t2,…,tend).

B. Moyenne des potentiels évoqués auditifs des sujets contrôles en réponse à la première (t1, déviant, en rouge) et onzième (t11, standard, en vert) présentation de son, sur une carte cérébrale EEG composée de 60 électrodes. C. Potentiels évoqués auditifs en réponse aux sons standards (vert) et déviants (rouge) au niveau de l'électrode Cz (centrale) chez les sujets contrôles (Boly *et al.*, 2011a).

Au niveau du scalp, les sujets contrôles et les patients en état de conscience minimale présentaient des composantes de longue latence avec une topographie centrale (la figure 5B&C illustre la réponse des sujets contrôles). Les latences du pic pour la négativité de discordance étaient de 170 ms chez les sujets contrôles et de 175 ms chez les patients en état de conscience minimale. Alors que la négativité de discordance était la plus importante chez les patients en état de conscience minimale, c'est la composante P3 (latence du pic de 250 ms) qui était la plus notable chez les participants contrôles (figure 5 et 6). Seules les composantes postérieures précoces (pic à 55 ms) étaient perceptibles chez les patients en état d'éveil non-répondant (figure 6). Nous avons aussi constaté une interaction significative entre le niveau de conscience et l'amplitude des réponses de longue latence (figure 6), confirmant des résultats obtenus précédemment chez des sujets récupérant d'un syndrome d'éveil non-répondant, d'une anesthésie ou du sommeil (Heinke *et al.*, 2004; Wijnen *et al.*, 2007; Ruby *et al.*, 2008).

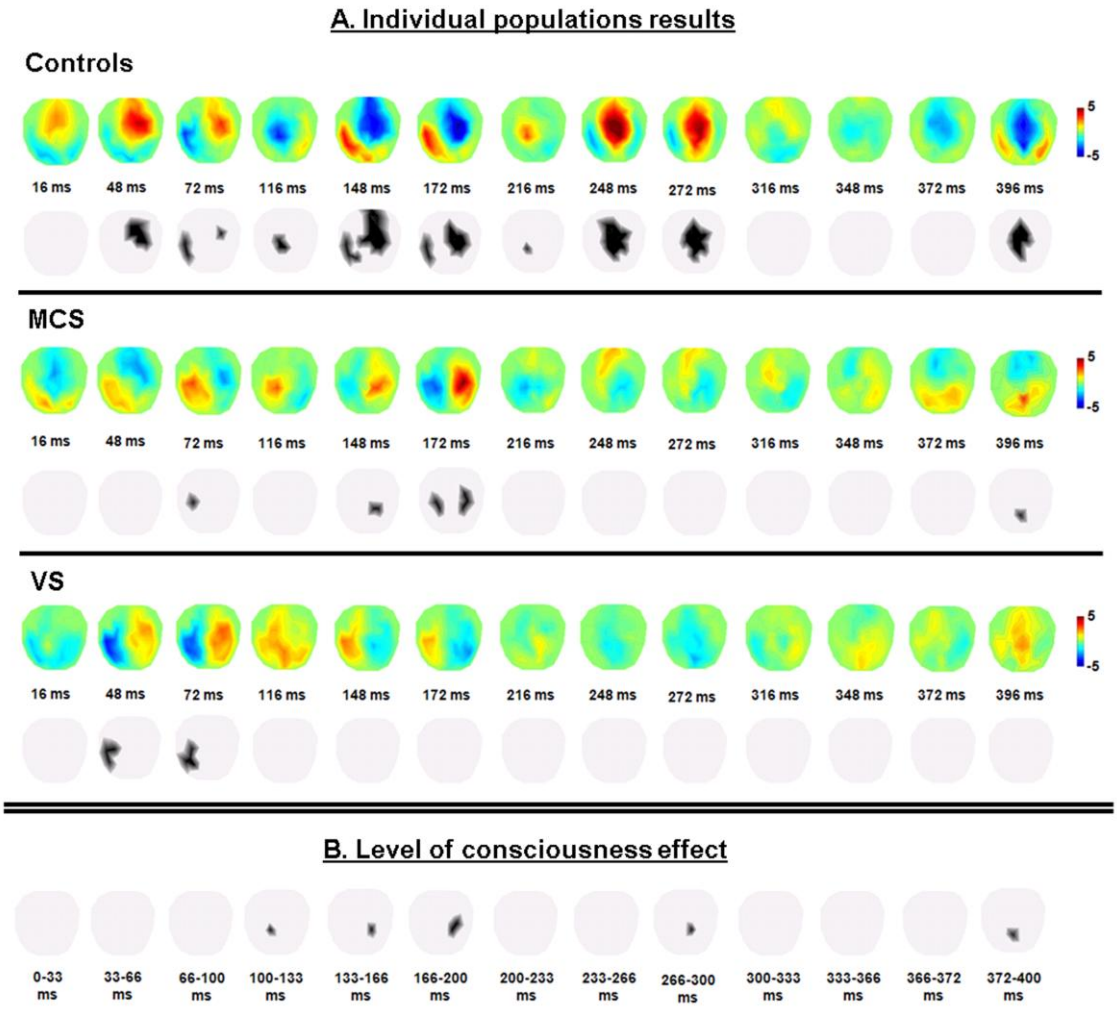


Figure 6. Moyenne des différences spatiotemporelles entre les sons standards et déviants en fonction du niveau de conscience. A. Cartes des réponses différentielles moyennes des contrôles sains, des patients en état de conscience minimale (MCS) et en syndrome d'éveil non-répondant (VS). Les images en couleur correspondent aux valeurs statistiques T et en noir et blanc aux voxels significatifs. B. Cartes montrant les régions au niveau du scalp où il y a une interaction significative entre l'amplitude des réponses et le niveau de conscience sur différentes fenêtres temporelles (Boly *et al.*, 2011a).

Dans un deuxième temps, pour inférer les mécanismes neuronaux qui sous-tendent les réponses évoquées observées, nous avons eu recours à une analyse DCM qui emploie des modèles neuronaux de masse et des statistiques bayésiennes (David *et al.*, 2005; Friston, 2009; Kiebel *et al.*, 2009). Ce type d'analyse a déjà été validé dans le cadre de plusieurs autres études en EEG (Garrido *et al.*, 2007; 2008; 2009). Pour optimiser sa reconstruction de source, la DCM cherche des différences sous la forme de PE sur tout le temps péri-stimulus (Garrido *et al.*, 2007; Boly *et al.*, 2011b). Chez les volontaires sains, l'anatomie fonctionnelle suscitée par le paradigme employé comprend des connexions antérogrades et rétrogrades dans un réseau cortical fronto-temporal (Garrido *et al.*, 2008). Chez les patients gravement cérébrolésés, l'implication du cortex frontal via ses connexions antérogrades et rétrogrades

doit encore être démontrée. Nous avons donc identifié l'architecture du réseau qui expliquait le mieux les réponses chez nos patients, en comparant 11 modèles qui différaient selon les régions (cortex auditifs primaires bilatéraux, gyrus temporal supérieur bilatéral, cortex frontal inférieur droit) et les connexions concernées (antérogrades, rétrogrades). Le modèle qui pouvait le mieux expliquer les réponses chez les patients inclut une source frontale avec des connexions antérogrades et rétrogrades, comme chez les contrôles sains (figure 8). Le seul effet notable du niveau de conscience s'exerçait sur la connexion rétrograde du cortex frontal au cortex temporal supérieur (p=0.012) (figure 8). Cette connexion rétrograde était considérablement diminuée chez les patients en état d'éveil non-répondant par rapport aux sujets contrôles (p=0.002) et aux patients en état de conscience minimale (p=0.001). Ces derniers présentaient, quant à eux, une connectivité descendante préservée qui ne différait pas significativement de celle des participants contrôles (p>0.05, figure 8).

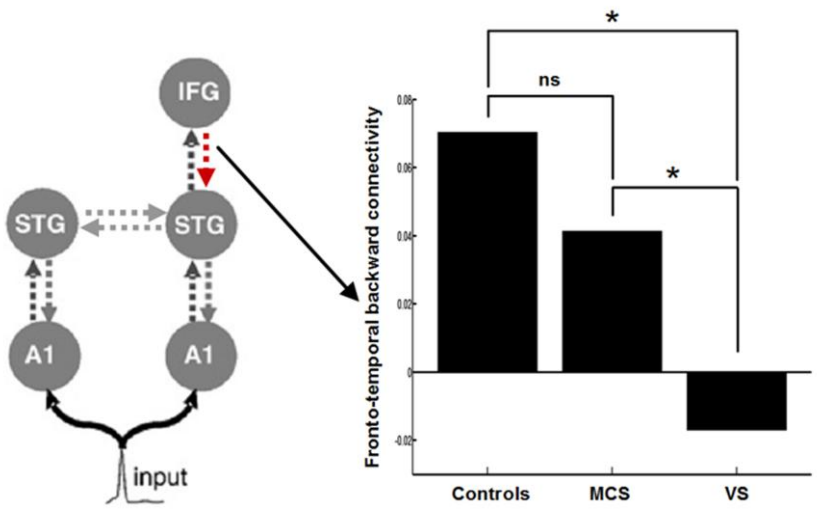


Figure 8. Analyse quantitative de la connectivité effective. La seule différence significative (*) entre les patients en état d'éveil non-répondant et les sujets contrôles est un déficit dans les connexions descendantes (en rouge) du cortex frontal (IFG: gyrus frontal inférieur) au cortex temporal (STG: gyrus temporal supérieur). Les patients en état de conscience minimale montrent quant à eux une connectivité comparable aux sujets contrôles. A gauche: modèle de la propagation de l'information auditive (A1 : cortex auditif primaire). A droite: moyenne des paramètres d'estimation de connectivité pour les trois groupes (état d'éveil non-répondant – VS, état de conscience minimale – MCS et contrôle) (Boly et al, 2011a).

Le cortex frontal semble donc être impliqué dans la production des PE chez les patients en état d'éveil non-répondant, avec cependant une anomalie dans le traitement récurrent des cortex d'ordre supérieur, en raison de connexions rétrogrades diminuées entre les cortex frontaux et temporaux. Ce résultat suggère que les causes pathophysiologiques du syndrome d'éveil non-répondant trouvent une expression commune dans la réduction des

influences descendantes fronto-temporales (cela n'exclut toutefois pas des dysfonctions cérébrales plus étendues chez certains patients). Contrairement à ces derniers, les patients en état de conscience minimale présentaient des composantes de longue latence et une connectivité effective récurrente proche de la normale. Cette différence entre les groupes ne peut être attribuée à des différences de vigilance, étant donné que tous les patients étaient maintenus dans le même état d'éveil tout au long de l'expérience. Ces observations soulignent l'importance probable du traitement récurrent dans les aires corticales d'ordre supérieur pour engendrer une perception consciente (Crick et Koch, 1995; Dehaene *et al.*, 2006).

L'analyse de la connectivité corticale semble donc être plus spécifique que les analyses au niveau du scalp en termes de détection des corrélats architecturaux du niveau de conscience. D'un autre côté, nos analyses ne peuvent pas déterminer si un déficit de la connectivité rétrograde de la région frontale est une cause ou une conséquence du traitement qui sous-tend la conscience. Ce que nous pouvons affirmer, c'est qu'une défaillance spécifique (descendante) de la connectivité effective est impliquée dans la conscience mais rien ne permet de supposer que les réponses obtenues dans ce paradigme soient liées à la perception consciente des stimuli utilisés. En effet, les changements observés dans l'architecture du réseau sont ici liés au niveau de conscience et non pas au contenu (perception d'un son particulier). Enfin, il est également probable que cet outil nous informe sur le pronostic des patients. En effet, au niveau du scalp, nous avons obtenu une corrélation significative entre les réponses différentielles (standard – déviant à une latence de 115 ms) et le pronostic des patients en état d'éveil non-répondant ($p<0.05$, résultat non publié). Cet effet était en fait provoqué par l'existence d'une réponse paradoxalement élevée aux stimuli standards chez les patients en état d'éveil non-répondant récupérant une communication fonctionnelle, par rapport aux patients ne présentant aucune récupération.

En résumé, nos résultats ont montré qu'une perturbation sélective des processus rétrogrades dans les niveaux supérieurs de la hiérarchie corticale peut mener à une perte de conscience chez les patients cérébrolésés. La présente approche pourrait constituer un nouvel outil diagnostique (et pronostique) pour quantifier le niveau de conscience au chevet des patients en état de conscience altérée. D'autres études sont nécessaires pour confirmer ces résultats préliminaires et pour déterminer les mécanismes moléculaires ou physiologiques précis qui sous-tendent ces observations, notamment en étudiant d'autres états de conscience altérée tels que le sommeil, l'épilepsie ou l'anesthésie.

3.4 Conclusion

Contrairement aux études par IRM et TEP, les études par EEG permettent d'étudier l'activité cérébrale avec une très bonne résolution temporelle. Cette haute résolution paraît nécessaire pour déterminer la dynamique de la génération d'une activité neuronale susceptible de mener à une activité consciente, typiquement suggérée de l'ordre de quelques centaines de millisecondes (Tononi, 2008). Malgré un accroissement considérable des études sur les corrélats électrophysiologiques de la conscience, ces derniers restent toutefois relativement peu connus. Nous avons montré une diminution de la complexité des réseaux neuronaux en fonction du niveau de conscience des patients en état de conscience altérée (Gosseries *et al.*, 2011b), et plus spécifiquement une défaillance de la connectivité rétrograde effective chez les patients en état d'éveil non-répondant (Boly *et al.*, 2011a). Ces études fournissent une aide au diagnostic avec une technique « facile » qui peut être utilisée en clinique lorsque le diagnostic d'un patient est incertain (avec toutefois encore un risque d'erreur) et une technique plus complexe qui nécessite néanmoins encore une validation au niveau individuel et au niveau du pronostic. Nous sommes donc actuellement en train d'acquérir de nouvelles données longitudinales sur une large cohorte de patients récupérant du coma, et ce, en améliorant le rapport signal sur bruit (c.-à.-d. deux sessions de 15 minutes au lieu d'une). Il est également nécessaire de mettre au point d'autres études sur le sommeil et l'anesthésie, et de recourir à d'autres paradigmes de potentiels évoqués pour confirmer nos constatations.

Nos résultats sont en accord avec les théories neuroscientifique de la conscience. En effet, les patients en état de conscience altérée présentent une perte d'intégration de l'information reflétée par i) une diminution de la complexité cérébrale (mesure globale d'entropie), ii) une réduction de la durée de l'activité cérébrale (réponse aux sons de moins de 100 ms chez les patients en état d'éveil non-répondant *versus* plusieurs centaines de millisecondes chez les patients en état de conscience minimale) et iii) un déficit spécifique dans les connexions descendantes entre les cortex associatifs frontaux et temporaux lors du traitement de stimuli auditifs. Pour approfondir ces recherches, nous pourrions étudier la non-linéarité des réponses cérébrales afin d'apprécier la complexité cérébrale chez les patients en état de conscience altérée, par exemple au moyen des interactions de fréquence croisées entre les aires cérébrales en réponse à des stimuli auditifs (Ahrens *et al.*, 2008). En présence de dynamiques bistables et d'une perte de différenciation corticale, on s'attendrait à ce que l'activité dans une région du cerveau produise un tracé d'activité cérébrale similaire, avec un contenu de fréquence similaire, dans les régions environnantes (Massimini *et al.*, 2011). Le

tracé d'activité cérébrale serait très différent en présence d'une activité modulée progressive, comme celle observée à l'état conscient (Alkire *et al.*, 2008). Il est à noter que des études antérieures ont indiqué la prépondérance de non-linéarité dans les connexions rétrogrades, par rapport aux connexions antérogrades (Chen *et al.*, 2009). L'intégrité des connexions rétrogrades pourrait donc être plus ou moins directement liée à une complexité préservée de l'activité cérébrale chez les patients en état de conscience altérée. D'autres études devraient examiner cette dernière hypothèse plus en détail (Boly *et al.*, sous presse).

CHAPITRE 4. STIMULATION MAGNETIQUE TRANSCRANIENNE COMME MESURE DES CONNEXIONS CORTICO-SPINALES

La véritable science enseigne, par-dessus tout, à douter et à être ignorant » (Miguel de Unamun)

Sur base des articles suivants:

Lapitskaya N, Gosseries O, Delvaux V, Overgaard M, Nielsen F, Maertens de Noordhout A, Moonen G, Laureys S. Transcranial magnetic stimulation in disorders of consciousness. *Reviews in the Neuroscience*, 20(3-4): 235-50, 2009.

Gosseries O* & Lapitskaya N* (*co-premières), De Pasqua V, Pedersen A, Nielsen JF, Maertens de Noordhout A, Laureys S. Abnormal cortico-spinal excitability in patients with disorders of consciousness. *Soumis.*

4.1 Introduction

La stimulation magnétique transcrânienne (SMT) est une technique non invasive qui permet de stimuler le cortex cérébral en produisant un champ magnétique bref créé par un courant électrique circulant dans une bobine placée sur le scalp (Barker et Jalinous, 1985). Ce champ magnétique pénètre dans les tissus cérébraux et induit un courant électrique qui dépolarise les neurones (Di Lazzaro *et al.*, 2004). Selon les paramètres de stimulation (ex : localisation, intensité et fréquence du stimulus), la SMT peut activer divers réseaux cortico-corticaux et cortico-sous-corticaux, les inhiber ou interférer avec leur activité. Les effets de la SMT durent le temps de la stimulation mais peuvent également induire des changements cérébraux à plus long terme si les stimulations sont répétées à une certaine fréquence. Classiquement, le cortex moteur primaire est stimulé et les potentiels évoqués moteurs (PEM) sont enregistrés au niveau musculaire à l'aide d'électrodes d'électromyographie de surface. Les stimulations peuvent être simples, doubles ou répétées. Les impulsions simples sont appliquées sur le cortex moteur pour déterminer le seuil d'excitabilité (seuil moteur au repos) qui correspond à l'intensité minimale de stimulation nécessaire pour induire des PEM au niveau du muscle testé, et ce, pour au minimum 50% des essais. Des impulsions simples d'intensité progressivement croissante peuvent aussi servir à générer des courbes de recrutement. Dans le cas d'un paradigme à double impulsion, selon l'intervalle de temps entre les deux impulsions, la SMT provoque une inhibition (1-6 ms) ou une facilitation intra-corticale motrice (10-15 ms) (Lapitskaya *et al.*, 2009a).

La SMT peut également être employée pour étudier les interactions entre le cortex moteur primaire et le cortex sensoriel. Il a été démontré que l'influx afférent (c.-à-d. la stimulation électrique des nerfs médians) modifie l'excitabilité du cortex moteur induite peu de temps après par la SMT, avec un déroulement temporel complexe (Maertens de Noordhout *et al.*, 1992; Tokimura *et al.*, 2000). Ce phénomène est dénommé « inhibition afférente à courte latence ». La connectivité fonctionnelle entre les deux hémisphères cérébraux peut aussi être étudiée au moyen d'une SMT transcallosale en appliquant un stimulus « conditionné » à l'un des hémisphères et un stimulus « test » à l'autre hémisphère (Ferbert *et al.*, 1992). Ce processus est généralement appelé « inhibition interhémisphérique » (Wassermann *et al.*, 1991; Gerloff *et al.*, 1998). Enfin, la SMT répétitive consiste en une série d'impulsions multiples appliquées à une fréquence particulière qui produit des effets prolongés dans le cerveau. Les fréquences de stimulations inférieures à 1 Hz tendent à réduire l'excitabilité du cortex cérébral (Chen *et al.*, 1997; Romero *et al.*, 2002), alors que les

fréquences supérieures à 1Hz permettent d'accroître cette excitabilité (Berardelli *et al.*, 1998). Comme la SMT répétitive peut potentiellement induire une crise épileptique, des limites de sécurité ont été publiées quant à son utilisation sur des sujets humains (Wassermann, 1998; Wassermann et Lisanby, 2001).

Au cours des deux dernières décennies, la SMT a permis de mieux comprendre les mécanismes physiologiques et les conséquences de la réorganisation corticale motrice dans le cerveau humain intact ou lésé. Les études qui ont porté sur les lésions cérébrales sévères entrainant des troubles de la conscience sont cependant rares (Lapitskaya *et al.*, 2009b). Chez les patients diagnostiqués en mort cérébrale, deux études utilisant la SMT à impulsion simple ont montré une absence de réponse motrice (Firsching *et al.*, 1992; Ying *et al.*, 1992). Dans la phase aiguë après un coma, les patients présentent des résultats hétérogènes, allant d'une absence de réponse bilatérale à une réponse unilatérale ou bilatérale, retardée ou non (Schwarz *et al.*, 2000). Une corrélation a été mise en évidence entre les PEM et le pronostic clinique des patients (Facco *et al.*, 1991; Ying *et al.*, 1992; Zentner et Rohde, 1992). Deux autres études ont évalué les fonctions motrices chez des patients en état d'éveil non-répondant et en état de conscience minimale. Moosavi et ses collègues (1999) ont appliqué une SMT par impulsion simple au niveau du cortex moteur de 19 patients. Onze patients étaient considérés en état d'éveil non-répondant et huit en état de conscience minimale (6 à 76 mois post anoxie). Une absence de PEM a été observée chez deux patients en état d'éveil non-répondant, alors qu'un seuil moteur plus élevé et une irrégularité plus importante dans la forme des PEM caractérisaient les neuf autres patients en état d'éveil non-répondant (comparés aux patients en état de conscience minimale). Une deuxième étude a évalué de manière longitudinale 27 patients diagnostiqués initialement en état d'éveil non-répondant (évaluations à 2, 6 et 12 mois après le traumatisme cérébral) (Mazzini *et al.*, 1999). Les résultats ont montré une tendance générale à une augmentation de l'amplitude et à une diminution de la latence des PEM au cours du temps. Aucune valeur pronostique des PEM n'a par contre été observée. Enfin, dans une étude portant sur six cas de locked-in syndrome, les PEM étaient absents chez quatre patients. Ceux-ci n'ont ensuite montré aucune récupération clinique. À l'inverse, des PEM ont été observés chez deux patients qui ont par la suite récupéré une fonction motrice presque complète (Bassetti *et al.*, 1994).

Ces études corroborent l'idée qu'il subsiste un certain degré d'intégrité fonctionnelle corticale chez les patients en état de conscience altérée, même lorsque le diagnostic clinique est celui d'un état d'éveil non-répondant (Laureys *et al.*, 2004b). Le diagnostic d'état de

conscience altérée n'est toutefois pas bien défini dans ces études, notamment parce qu'elles ont été menées avant l'introduction des critères diagnostiques de l'état de conscience minimale (Giacino *et al.*, 2002). De plus, les paradigmes de stimulation par impulsion simple apportent certaines informations sur l'intégrité des connexions cortico-spinales mais les paradigmes de stimulation par impulsion double pourraient évaluer davantage les réseaux moteurs inhibiteurs et excitateurs et les connexions cortico-corticales chez les patients cérébrolésés. Par exemple, l'inhibition afférente à courte latence pourrait être explorée comme marqueur de connectivité entre les aires motrices et sensorielles. Dans la seconde partie de ce chapitre, nous allons évaluer différents paramètres moteurs, par stimulations simples et doubles, chez des patients en état d'éveil non-répondant, en état de conscience minimale et chez des sujets contrôles sains afin de mieux comprendre les mécanismes pathophysiologiques impliqués dans les troubles de la conscience. Nous formulons l'hypothèse qu'il existerait une corrélation positive entre l'excitabilité cortico-spinale et la gravité des lésions cérébrales. Nous nous attendons plus particulièrement à observer une différence dans les mesures corticales en fonction du niveau de conscience.

4.2 Excitabilité cortico-spinale anormale chez les patients en état de conscience altérée

Nous avons examiné les voies cortico-spinales de 47 patients sévèrement cérébrolésés (21 cas d'étiologie traumatique). Vingt-trois de ces patients ont été diagnostiqués en état d'éveil non-répondant (16 hommes, âgés de 45±22 ans; 17±54 mois post-lésion, 9 cas d'étiologie traumatique) et 24 en état de conscience minimale (19 hommes, âgés de 41±17 ans, 36±67 mois post-lésion, 11 cas d'étiologie traumatique) au moyen de la CRS-R. Quatorze volontaires sains ont également été recrutés (8 hommes, âgés de 33±10 ans).

Les enregistrements électromyographiques ont été effectués sur le premier muscle dorsal interosseux bilatéralement. Les mesures de base incluaient les ondes M (c.-à-d., la première contraction des fibres musculaires à la suite d'une stimulation électrique du nerf ulnaire), les ondes F (c.-à-d., la décharge récurrente des neurones moteurs spinaux à la suite de cette même stimulation), le temps de conduction moteur périphérique et central, et les potentiels évoqués somatosensoriels. Le cortex moteur primaire (le « *hotspot* » se situant au niveau de l'aire corticale représentant la main) a été stimulé bilatéralement au moyen d'une bobine de type « figure en huit » (Magstim Company Ltd, U.K.). Nous avons évalué l'intensité du seuil moteur au repos (SMR), la latence et l'amplitude des MEP (stimulation simple), les courbes stimulus/réponse et l'inhibition afférente à courte latence. Le SMR a été

défini comme l'intensité minimale de la SMT, exprimée en pourcentage de l'intensité maximale du stimulateur, capable de susciter cinq PEM d'au moins 50µV d'amplitude lors de dix essais consécutifs (Rossini *et al.*, 1999). Les courbes de recrutement ont été mesurées en partant du SMR et en augmentant l'intensité de la stimulation jusqu'à 40 % au-dessus du SMR, par degré de 10 % avec cinq essais par intensité (Bernabeu *et al.*, 2009). L'inhibition afférente à courte latence a été obtenue au moyen d'une stimulation électrique du nerf médian et d'une stimulation du cortex moteur controlatéral. Nous avons utilisé neuf intervalles inter-stimuli entre les deux stimulations (intervalles partant de la latence N20 -2 ms à N20 +14 ms, par degré de 2 ms) (Fujiki *et al.*, 2006). L'intensité du stimulus électrique était légèrement supérieure au seuil moteur pour le muscle court abducteur du pouce, et le stimulus cortical avait une intensité de 120 % du SMR. Chaque bloc comportait 50 stimuli aléatoires dont cinq stimulations corticales simples et cinq stimulations doubles pour chaque intervalle inter-stimuli, avec un intervalle de huit secondes entre les essais. Toutes les réponses ont été enregistrées au moyen du logiciel Signal (version 4.1, Cambridge). Les analyses statistiques ont été réalisées avec STATA (version 9.2, Texas) et SAS (version 9.1, Cary) incluant des tests de Kruskal-Wallis, de Mann-Whitney et un modèle linéaire mixte. Les résultats ont été considérés significatifs à partir de $p<0.05$ (pour des informations méthodologiques supplémentaires, voir Gosseries & Lapitskaya *et al.*, soumis).

Le tableau 7 résume les caractéristiques cliniques et les mesures électro-physiologiques de base pour les trois groupes. Pour les mesures spinales, seule une différence a été observée pour l'onde M maximale entre les patients et les sujets contrôles ($p<0.001$). Cette différence peut s'expliquer par une atrophie musculaire liée à une absence de mouvements chez les patients. Les ondes F et les temps de conduction n'étaient pas différents entre les groupes, comme précédemment observés par Moosavi et al (1999). Ceci suggère que les déficits moteurs peuvent exister malgré des temps de conduction cortico-motoneuronal normaux (Homberg *et al.*, 1991). Pour les mesures corticales, aucun PEM n'a pu être détecté chez quatre patients en état d'éveil non-répondant et chez un patient en état de conscience minimale. Les PEM étaient présents uniquement dans un hémisphère chez cinq en état d'éveil non-répondant et chez sept patients en état de conscience minimale. L'amplitude des MEP différait entre les patients et les sujets contrôles ($p<0.05$) et entre les patients en état d'éveil non-répondant et ceux en état de conscience minimale ($p=0.02$). De plus, le SMR était plus élevé chez les patients par rapport aux sujets sains ($p<0.001$). Ces résultats sont en accord avec des études antérieures sur des patients récupérant d'une anoxie et de lésions cérébrales

traumatiques diffuses (Chistyakov *et al.*, 1998; Moosavi *et al.*, 1999; Bernabeu *et al.*, 2009). Le SMR paraît représenter une mesure de l'excitabilité de la membrane des neurones pyramidaux (Ziemann *et al.*, 1996) et semble fortement corrélé avec la maturation, la myélinisation et l'intégrité structurelle de la matière blanche des cortex moteur primaire et prémoteur (Kloppel *et al.*, 2008). Le SMR est également conditionné par l'excitabilité des motoneurones spinaux puisque l'activation de ceux-ci est aussi nécessaire pour produire un PEM au niveau du muscle (Siebner et Rothwell, 2003). Nos résultats ont cependant montré une relative préservation de l'onde F chez les patients, ce qui suggère que l'augmentation du SMR observée chez les patients est due à une diminution de l'excitabilité corticale.

Variables	**Healthy** (n=14)	**MCS** (n=24)	**VS/UWS** (n=23)
Age (years)	32.7±10.3	40.7±17.2	45.0±22.3
Time since injury (months)	/	35.9±66.8	16.9±53.6
CRS-R total score (points)	/	13.3±4.8	4.4±1.3
CRS-R motor score (points)	/	3.4±1.6	1.2±0.7
Mmax (mV)	10±2.3	4.8±2.0*	5.1±2.9*
F-wave persistence (number)	13.5±5.1	16.1±5.8	17.4±4.4
SEP latency (ms)	19.3±1.1	20.4±1.8	20.2±2.0
MEP latency (ms)	22.3±1.2	22.5±2.2	22.8±2.4
PMCT (ms)	16.4±1.2	16.7±1.8	16.6±1.6
CMCT (ms)	5.9±1.2	6.2±2.6	6.7±3.3
RMT (% MSO)	39.3±7.6	49.1±18.9	50.9±13.3*
Unconditioned MEP paired-Pulse paradigms (mV)	7.4±6.1	8.8±7.5	4.35±5.9*†

Tableau 7. Caractéristiques cliniques et électrophysiologiques des patients en état d'éveil non-répondant (VS), en état de conscience minimale (MCS) et chez des sujets contrôles (valeur moyenne ± déviation standard). Abréviation: M-max, amplitude maximale des ondes M; F-wave persistence, nombre d'ondes F avec une amplitude d'au moins 20 μV sur 20 ondes F; PMCT, temps de conduction périphérique ; CMCT, temps de conduction central; SEP, potentiels évoqués somatosensoriels; MEP, potentiels évoqués moteurs; RMT, seuil moteur au repos; %MSO, pourcentage de l'intensité maximale du stimulateur. *Différence significative avec les sujets contrôles. † Différence avec les patients en état de conscience minimale ($p<0.05$) (Gosseries & Lapitskaya *et al.*, soumis).

Les courbes stimulus/réponse présentaient une augmentation graduelle de l'amplitude des PEM, avec l'accroissement de l'intensité des stimulations (figure 10). Les courbes étaient plus larges en fonction du niveau de conscience (normal > état de conscience minimale > état d'éveil non-répondant, $p<0.0001$). Des résultats similaires ont été obtenus chez des patients présentant de graves lésions cérébrales traumatiques par rapport à des sujets sains (Bernabeu

et al., 2009). Nos résultats mettent également en évidence une différence entre les patients en état d'éveil non-répondant et les patients en état de conscience minimale ($p<0.005$). Ces courbes permettent d'évaluer des neurones qui sont intrinsèquement moins excitables ou plus éloignés du centre d'activation (Vallssole *et al.*, 1994) et pourraient refléter la taille de la représentation corticale ainsi que la distribution de l'excitabilité dans les projections cortico-spinales (Siebner et Rothwell, 2003). De plus, l'augmentation de l'amplitude des PEM étaient associées aux valeurs initiales du SMR ($r=-0.20$, $p=0.0016$). Des valeurs de SMR élevées étaient plus susceptibles de provoquer des valeurs manquantes de PEM, en dépassant la limite maximale de l'influx stimulateur.

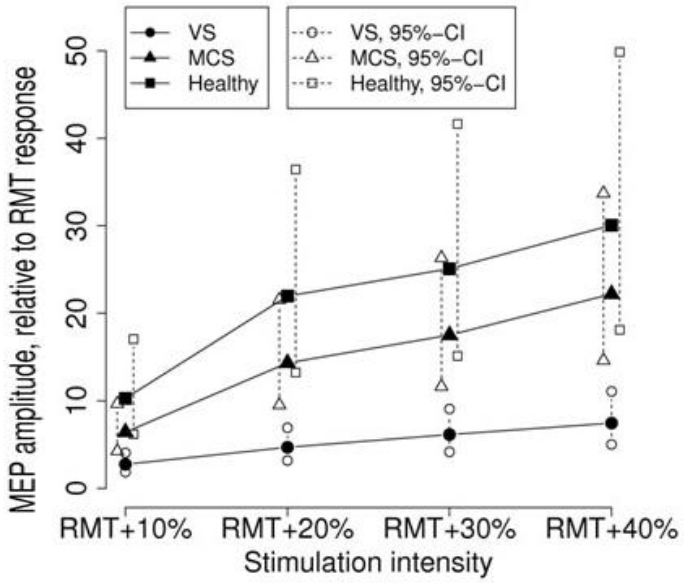


Figure 10. Courbe de recrutement chez les patients en état d'éveil non-répondant (VS, ronds noirs), en état de conscience minimale (MCS, triangles noirs) et chez des sujets contrôles (healthy, carrés noirs). Les symboles blancs représentent l'intervalle de confiance (95%). L'intensité de la stimulation est exprimée par le pourcentage de l'influx stimulateur maximal au-dessus du seuil moteur (RMT) (Gosseries & Lapitskaya *et al.*, soumis).

Enfin, nos résultats ont mis en évidence une différence d'inhibition afférente à courte latence entre les groupes ($p<0.0001$, figure 11). Chez les sujets contrôles, les réponses motrices étaient les plus inhibées lorsque l'intervalle entre la stimulation électrique périphérique et la stimulation corticale correspondait à la latence de la réponse N20 +2ms ($p=0.0001$), comme observé précédemment (Fischer et Orth, 2011). A cet intervalle, les valeurs médianes des PEM chez les participants contrôles était de 31% de la taille du stimulus test (stimulation corticale simple), de 81% chez les patients en état de conscience minimale et de 97% chez les patients en état d'éveil non-répondant. Une différence significative a été mise en évidence entre les sujets sains et les patients ($p<0.001$) mais pas entre les deux groupes de

patients (p=0.7). Par ailleurs, une corrélation entre l'inhibition afférente à courte latence (à N20+2 ms) et le niveau de conscience des patients (scores totaux à la CRS-R) a été observée (figure 11, r=-0.39 ; p=0.02).

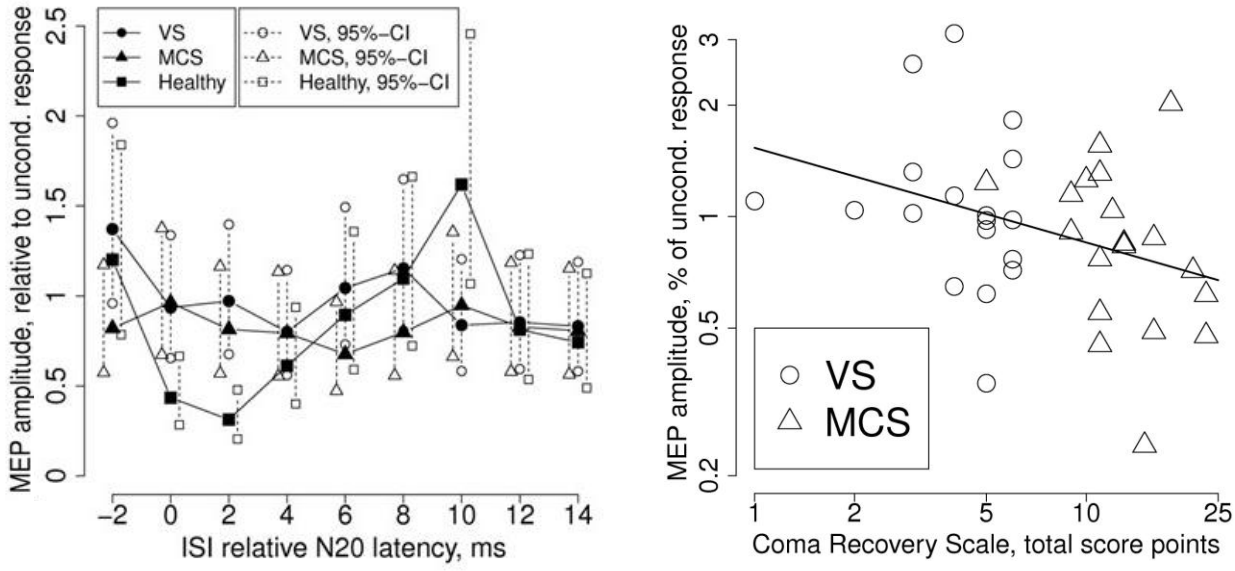


Figure 11. A gauche : Inhibition afférente à courte latence chez les patients en état d'éveil non-répondant (VS, rond noir), en état de conscience minimale (MCS, triangle noir) et chez des sujets contrôles (healthy, carré noir). En abscisse, les différents intervalles (ISI) entre la stimulation du nerf médian et la stimulation du cortex moteur primaire controlatéral, ajustés selon la latence de la réponse somatosensorielle N20 individuelle. En ordonnée, moyennes des réponses motrices (MEP amplitude) relatives à la réponse inconditionnée (stimulation simple). A droite : Corrélation avec le niveau de conscience des patients. L'amplitude des réponses motrices individuelles à l'intervalle N20 +2ms est corrélée aux scores totaux de la CRS-R. Les ronds représentent les patients en état d'éveil non-répondant (VS) et les triangles les patients en état de conscience minimale (MCS) (Gosseries & Lapitskaya *et al.*, soumis).

Ces derniers résultats rejoignent des études antérieures qui ont montré une diminution de l'inhibition afférente à courte latence chez des patients conscients ayant subi des lésions cérébrales axonales traumatiques et anoxiques diffuses (Fujiki *et al.*, 2006, Lapitskaya *et al.*, sous presse) et chez des patients atteints de déficits cognitifs modérés ou de la maladie d'Alzheimer (Di Lazzaro *et al.*, 2008; Nardone *et al.*, 2011). Une étude récente a également montré une corrélation entre le niveau d'inhibition et la récupération à long terme après un accident vasculaire cérébral aigu (Di Lazzaro *et al.*, 2012). Les mécanismes sous-jacents de l'inhibition afférente à courte latence ne sont à l'heure actuelle pas entièrement compris. Certains éléments suggèrent que cette inhibition est un phénomène cortical (Tokimura *et al.*, 2000) qui pourrait être lié à l'activité cholinergique centrale (Di Lazzaro *et al.*, 2002; Di Lazzaro *et al.*, 2006). De fait, il a été démontré que l'administration d'inhibiteurs de

l'acétylcholinestérase améliore aussi bien l'inhibition afférente à courte latence en cas de lésion axonale diffuse que les capacités mnésiques lors de la réadaptation après une lésion cérébrale aiguë (Taverni *et al.*, 1998; Masanic *et al.*, 2001; Fujiki *et al.*, 2006).

Plusieurs limites de l'étude sont à souligner. Premièrement, les mesures de la SMT pourraient être influencées par des médicaments à action centrale (n=21). L'effet réducteur des benzodiazépines sur l'inhibition afférente à courte latence est connu (Di Lazzaro *et al.*, 2005), mais l'influence d'autres substances à action centrale n'a pas encore fait l'objet d'études approfondies. Toutefois, dans notre cohorte, les mesures de l'excitabilité corticale n'ont pas révélé de différences significatives liées à la prise de substances pharmacologiques. Un deuxième aspect concerne la fluctuation du niveau d'éveil qui est fréquemment rencontrée chez les patients en état de conscience altérée et qui pourrait éventuellement influencer les paramètres d'excitabilité corticale enregistrés. Afin de minimiser ce biais, nous avons appliqué un protocole standardisé de facilitation d'éveil (Giacino et al, 2004) chez les patients lorsque des signes de somnolence étaient observés. Troisièmement, une variabilité dans les réponses MEP a été observée au niveau intra-sujet et inter-sujet. Pour assurer une constance dans la répétition des différentes stimulations, nous avons marqué sur le scalp le point de stimulation. La localisation (en termes de millimètre) et l'orientation de la bobine sont toutefois sujettes à des imprécisions non mesurables sans système de neuronavigation. Ce système n'était malheureusement pas disponible au moment de l'étude mais nous en suggérons une utilisation systématique afin de diminuer la variabilité des PEM dues aux paramètres de stimulation. Enfin, la variabilité des PEM pourrait aussi être liée à l'hétérogénéité dans la taille, la localisation, la gravité et le type de lésions chez les patients. Des études ultérieures devraient mettre en corrélation les mesures d'inhibition avec l'anatomie cérébrale des patients (par ex. au moyen de l'imagerie par tenseur de diffusion).

4.3 Conclusion

L'évaluation des fonctions motrices fait partie intégrante de l'examen neurologique des patients récupérant du coma. La stimulation magnétique transcrânienne et l'électromyographie permettent d'évaluer objectivement les connexions cortico-spinales avec une haute résolution temporelle. Cette technique est facile à utiliser, rapide et peu coûteuse. Nous avons présenté ici la première évaluation détaillée de plusieurs mécanismes excitateurs et inhibiteurs chez les patients en état d'éveil non-répondant et en état de conscience minimale. Les mesures spinales périphériques étaient globalement similaires alors que les

mesures corticales différaient entre les sujets sains et les patients. Nos résultats ont principalement montré un seuil moteur plus élevé, des courbes stimulus/réponse de moindre amplitude et une réduction de l'inhibition afférente à courte latence chez les patients par rapport aux sujets sains, ce qui confirme le lien entre l'altération de l'excitabilité cortico-spinale et la présence de lésions cérébrales. De plus, les courbes de recrutement étaient différentes entre les deux groupes de patients et une corrélation a été observée entre l'inhibition afférente à courte latence et le niveau de conscience des patients (scores totaux à la CRS-R). Ces derniers résultats suggèrent donc un lien, probablement indirect, entre le niveau de conscience et l'altération des mécanismes cortico-spinaux et intra-corticaux, confirmant un syndrome de déconnexion corticale chez les patients en état de conscience altérée. Dans le prochain chapitre, nous utiliserons la SMT afin d'affiner les mesures de connexions cortico-corticales, et ce, en stimulant d'autres aires cérébrales que le cortex moteur et en enregistrant directement l'activité électrique cérébrale au moyen de l'EEG.

CHAPITRE 5. STIMULATION MAGNETIQUE TRANSCRANIENNE COUPLEE A L'ELECTROENCEPHALOGRAPHIE COMME MESURE DES CONNEXIONS CORTICO-CORTICALES

« La conscience de l'homme est une chose étrange, comme un feu que l'on croit éteint et qui se réveille » (Daniel Pennac)

Sur base des articles suivants:

Gosseries O* & Rosanova M* (*co-premiers), Casarotto S, Boly M, Casali AG, Bruno MA, Mariotti M, Boveroux P, Tononi G, Laureys S, Massimini M. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain*, sous presse, 2012.

Gosseries O* & Rosanova M* (*co-premiers), Boly M, Casarotto S, Napolitani M, Schnakers C, Bruno MA, Ledoux D, Massimini M, Laureys S. TMS-EEG in severely brain-injured patients: methodological aspects. *Soumis*.

5.1 Introduction

Comme nous l'avons vu précédemment, les déficits moteurs observés chez les patients souffrant de troubles de la conscience peuvent altérer leurs capacités à réaliser des mouvements volontaires (Schnakers *et al.*, 2009a). Des protocoles de neuroimagerie et d'électrophysiologie ont été mis au point afin de rechercher des signes de conscience, même chez les patients qui sont totalement incapables de bouger. Ces techniques manquent toutefois de sensibilité et l'absence de réponse ne peut pas être interprétée comme une absence de conscience. Il serait donc utile d'élaborer des méthodes plus sensibles pour détecter des signes de conscience au niveau individuel qui ne dépendent pas de l'intégrité des voies sensorielles et motrices, ni de la capacité du sujet à comprendre ou à exécuter des instructions. Il est possible d'y parvenir en recourant à la SMT couplée à l'EEG (Gosseries & Rosanova *et al.*, 2012). En plus de mesurer les connexions cortico-spinales, la SMT permet d'évaluer plus en détail les connexions cortico-corticales lorsqu'elle est combinée à l'EEG. La SMT-EEG permet en effet de détecter une connectivité effective en stimulant différents sous-ensembles de neurones corticaux et en mesurant les effets immédiats de cette activation initiale dans le reste du cerveau, avec une bonne résolution spatio-temporelle (Ilmoniemi *et al.*, 1997; Friston, 2002). Contrairement à la stimulation sensorielle, la stimulation corticale ne passe pas par le système réticulaire et contourne la porte thalamique. Cette technique teste donc directement la capacité des aires corticales à interagir entre elles, sans être biaisée par des effets périphériques. De plus, comme le sujet remarque à peine l'impulsion magnétique transcrânienne, les réponses neuronales ne sont pas contaminées par des réactions pouvant résulter de la prise de conscience de la stimulation cérébrale. Enfin, la SMT-EEG permet de dissocier la connectivité effective (interactions causales) de la connectivité fonctionnelle (corrélations temporelles).

Dans ce contexte, des études de connectivité effective durant les stades d'éveil et de sommeil profond ont été réalisées par Massimini *et al.* (2005). Chez les sujets sains en état d'éveil, la SMT induisait une réponse EEG prolongée, impliquant l'activation séquentielle de différentes aires cérébrales et affectant une grande partie du cortex. À l'inverse, durant le sommeil profond, les impulsions de la SMT produisaient une réponse simple qui restait circonscrite au site de stimulation. Cette observation indique une interruption des interactions effectives entre les modules thalamo-corticaux pendant le sommeil profond (Massimini *et al.*, 2005). Des résultats similaires ont été observés à la suite d'une anesthésie générale induite par midazolam (Ferrarelli *et al.*, 2010). Ces découvertes suggèrent que l'absence de conscience,

lors du sommeil profond et sous anesthésie générale, est liée à une diminution drastique de la connectivité corticale effective. Par contre, lors du sommeil paradoxal, quand les sujets ne répondent pas aux stimulations sensorielles et sont temporairement paralysés mais rapportent des rêves intenses au réveil, la réponse corticale à la SMT retrouvait sa complexité et était similaire à celle observée à l'état d'éveil (Massimini *et al.*, 2005).

5.2 Qu'en est-il des patients récupérant du coma?

En collaboration avec l'équipe du Pr. Massimini de l'Université de Milan, nous avons employé la SMT-EEG pour mesurer la connectivité effective au chevet de 17 patients récupérant du coma. Notre première hypothèse était que cette mesure de connectivité permettrait d'établir une distinction fiable entre les patients en état d'éveil non-répondant et les patients en état de conscience minimale. Notre seconde prédiction était que la restauration de la connectivité effective devrait être détectable chez les patients qui récupèrent progressivement une conscience et une communication fonctionnelle. Pour ce faire, nous avons stimulé bilatéralement le cortex frontal (gyrus frontal supérieur) et pariétal (gyrus pariétal supérieur) des patients et enregistré leurs réponses cérébrales électriques. Ces régions corticales ont été sélectionnées pour plusieurs raisons : i) elles sont aisément accessibles et éloignées des principaux muscles de la tête et du visage, dont l'activation non désirée peut affecter les enregistrements EEG ; ii) le cortex pariétal postérieur - ainsi que ses interactions avec les aires plus frontales - semblent jouer un rôle déterminant dans l'émergence de la conscience (Laureys *et al.*, 2004b; Vogt et Laureys, 2005; Hagmann *et al.*, 2008) et iii) des études antérieures ont employé la SMT-EEG dans ces régions d'intérêt durant les stades d'éveil (Rosanova *et al.*, 2009), de sommeil (Massimini *et al.*, 2007) et sous anesthésie générale (Ferrarelli *et al.*, 2010). Les cibles corticales ont été identifiées au moyen de CT scans (Siemens Senatom Sensation 16) et d'un système de neuronavigation (Navigated Brain Stimulation – NBS, Nexstim Ltd, Helsinki). Les stimulations ont été effectuées avec une bobine de type « figure en huit » (Eximia, Nexstim Ltd., Helsinki) à une intensité de 140 à 200 V/m sur la surface corticale. L'intervalle interstimuli variait aléatoirement entre 2 et 2.3 secondes (Rosanova *et al.*, 2009; Casarotto *et al.*, 2011).

Les enregistrements ont été réalisés avec un amplificateur EEG compatible avec la SMT et au moyen d'un casque EEG à 60 électrodes et de quatre électrodes faciales (Nexstim Ltd, Helsinki). Les artefacts provoqués par la stimulation trigéminale et par l'activité musculaire ont été minimisés en plaçant la bobine sur une région du scalp proche de la ligne

médiane. Les patients portaient des écouteurs qui diffusaient un bruit de masquage durant chaque session afin d'éviter que des réponses auditives au « clic » de la bobine ne contaminent les réponses (Rosanova *et al.*, 2009). Les analyses ont été effectuées au moyen du logiciel Matlab version R2006a (notamment avec SPM et Brainstorm). Chaque réponse évoquée par la SMT a été obtenue en faisant la moyenne de 150-250 essais dépourvus d'artefact. Pour obtenir la somme totale de l'activité électrique induite par la SMT, nous avons calculé la puissance globale du champ moyen (*global mean field power* – GMFP) (Lehmann et Skrandies, 1980). La localisation des courants neuronaux maximaux (10 sources les plus actives) sur la surface corticale a été détectée par modélisation de source, à tous les points significatifs lors des 300 premières millisecondes post-stimulus. Nous avons également enregistré l'activité électrique spontanée de chaque patient pendant cinq minutes. Pour plus de précisions sur les aspects méthodologiques, voir Gosseries & Rosanova *et al.* (2012).

Afin de tester si les mesures de connectivité effective permettent de faire la distinction entre les patients conscients et inconscients, nous avons évalué 12 patients récupérant du coma (5 femmes, âge 50±26 ans, 5 cas d'étiologie traumatique). Cinq patients ont été diagnostiqués en état d'éveil non-répondant, cinq étaient en état de conscience minimale et deux en locked-in syndrome. Ils ont été soumis à des évaluations comportementales répétées au moyen de la CRS-R. Le diagnostic clinique était clair et stable pour tous les patients. Onze patients se trouvaient en stade aigu et trois en stade chronique (>1 mois). Durant les acquisitions, les patients gardaient les yeux ouverts. Si des signes de somnolence apparaissaient, les enregistrements étaient momentanément interrompus afin de stimuler les patients au moyen du protocole de facilitation d'éveil. Pour plus de détails cliniques, voir Gosseries & Rosanova *et al.* (2012).

Chez les patients en état d'éveil non-répondant, la SMT a induit une réponse EEG lente positive-négative dans tous les cas, à l'exception d'un patient anoxique chez qui aucune réponse n'a été objectivée. Les courants corticaux maximaux sont restés localisés autour de l'aire stimulée et n'impliquait qu'un petit nombre de sources (figure 12A). Cette onde locale et stéréotypée se dissipait rapidement et était similaire à celle précédemment observée durant le sommeil profond et sous anesthésie générale. Les mesures SMT-EEG ont donc mis en évidence une diminution importante des interactions causales entre les aires cérébrales des patients en état d'éveil non-répondant. À l'inverse, chez tous les patients en état de conscience minimale, la SMT a provoqué une réponse électrique complexe qui se prolongeait dans le temps. Le schéma d'activation corticale évoluait rapidement, avec un déplacement progressif

des courants neuronaux maximaux du site stimulé vers un grand nombre de sources distantes (figure 12B). Cette réponse contraste fortement avec l'onde locale et simple enregistrée chez les patients en état d'éveil non-répondant et est plutôt comparable à la réponse obtenue chez les patients en locked-in syndrome (Figure 12C).

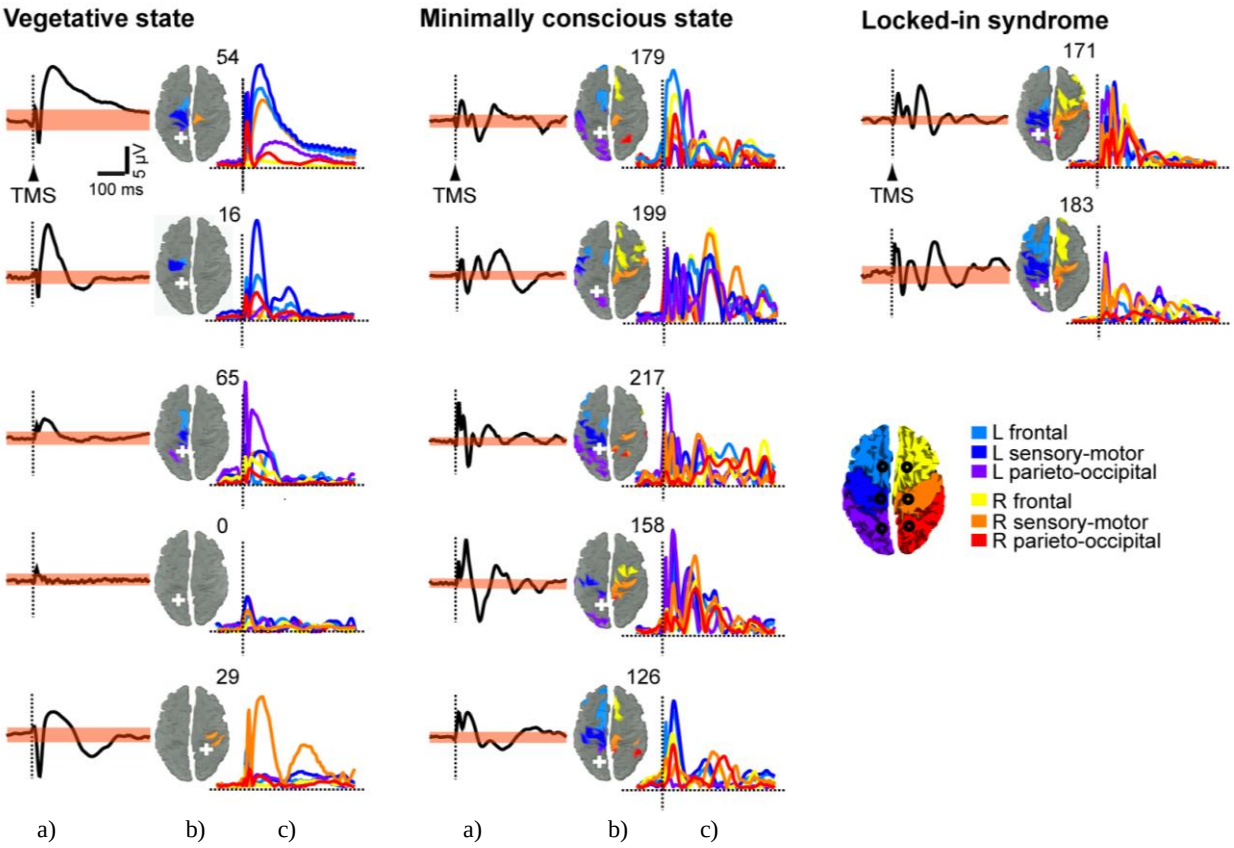


Figure 12. Réponses corticales induites par SMT chez cinq patients en état d'éveil non-répondant (vegetative state), cinq en état de conscience minimale (minimally conscious state) et deux en locked-in syndrome. a) Réponse moyennée (trace noire) de l'électrode en dessous du site de stimulation (cortex pariétal, croix blanche) avec le seuil significatif (bande rose) pour chaque patient. b) Les sources impliquées par les courants corticaux maximaux (dix sources les plus actives) sont coloriées en fonction de leur localisation sur le cortex cérébral (six macro-régions anatomiques comme indiqué dans la légende à droite); le nombre de sources détectées est indiqué en haut à droite de chaque image cérébrale. c) Les différentes traces de couleurs représentent les courants corticaux enregistrés à partir de six sources (cercles noirs dans la légende), une pour chaque macro-région. L = left; R = right (Gosseries & Rosanova *et al.*, 2012).

Les résultats obtenus ci-dessus pourraient être dictés par l'étendue des lésions structurelles, à savoir que les patients en état d'éveil non-répondant présentent des lésions anatomiques plus importantes que les patients en état de conscience minimale. Afin d'exclure cette possibilité et de vérifier si des changements de connectivité sont aussi détectables chez des patients qui reprennent graduellement conscience, nous avons ensuite suivi l'évolution temporelle de cinq patients (trois femmes, âge 51±23 ans, un cas d'étiologie traumatique ;

pour plus de détails, voir Gosseries & Rosanova *et al.*, 2012). Les patients ont été recrutés dans les services de soins intensifs et ont été évalués lorsqu'ils se trouvaient en syndrome d'éveil non-répondant, au moins 48 heures après l'arrêt de la sédation. Trois de ces patients ont ensuite été évalués lorsqu'ils évoluaient vers un état de conscience minimale et lorsqu'ils émergeaient de cet état. Les deux autres patients ont été réévalués un mois plus tard, toujours en état d'éveil non-répondant.

Au stade d'éveil non-répondant, la SMT a induit une onde lente, simple et locale chez tous les patients, excepté chez un qui n'a montré aucune réponse cérébrale (figure 13). Chez les deux patients qui n'ont pas présenté d'amélioration clinique significative, la seconde évaluation montrait à nouveau une réponse locale et simple chez un patient et aucune réponse chez l'autre (figure 13B). Chez les trois patients qui ont évolué vers un état de conscience minimale, une réponse d'activation complexe impliquant successivement un vaste ensemble d'aires corticales a été observée. Cette réponse était très différente de celle de la première évaluation et était plutôt comparable à celle de la troisième évaluation, quand les patients avaient récupéré une communication fonctionnelle (figure 13A). Une de ces patientes présentait des fluctuations importantes de la conscience, si bien que le jour de la seconde évaluation, elle était retombée temporairement en état d'éveil non-répondant (alors que le jour d'avant et le jour d'après, elle présentait des signes de conscience). Cette dernière observation suggère que la connectivité cérébrale pourrait rester établie malgré l'absence de réponses volontaires au niveau comportemental (figure 13A, session 2, VS).

Ces résultats indiquent que la perte de connectivité effective observée chez les patients en état d'éveil non-répondant peut être réversible et que la restauration de la communication interne dans le cerveau intervient à un stade qui précède la récupération fonctionnelle de la conscience, avant qu'une véritable communication puisse être établie avec le patient. La SMT-EEG fournirait également un indice de variation chez les patients en état de conscience minimale avec une fluctuation des réponses dans le temps et une absence de variation chez les patients en état d'éveil non-répondant.

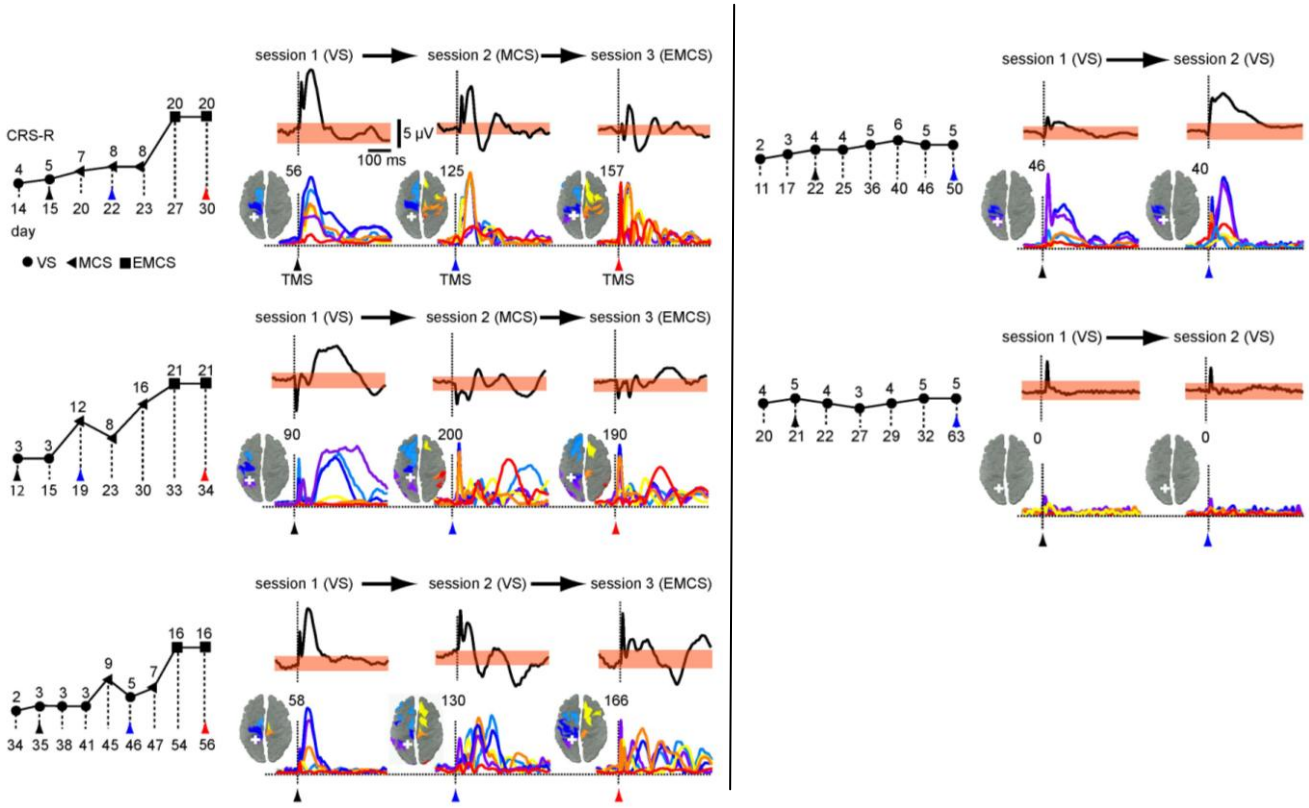


Figure 13. Evaluations cliniques et réponses corticales induites par SMT chez cinq patients suivis longitudinalement. Les scores totaux de la CRS-R sont illustrés en fonction du nombre de jours après l'accident cérébral chez les patients ayant récupéré une communication fonctionnelle (A) et chez ceux restés en état d'éveil non-répondant (B). Les symboles indiquent le diagnostic clinique associé (cercle = état d'éveil non-répondant - VS, triangle = état de conscience minimale – MCS et carré = sortie de l'état de conscience minimale - EMCS). Les flèches de couleur marquent les jours où les enregistrements SMT-EEG ont été effectués (noir = session 1; bleu = session 2; rouge = session 3). Voir légende de la figure 12 pour l'explication des autres illustrations (Gosseries & Rosanova *et al.*, 2012).

5.3 Dissociation entre les mécanismes de connectivité, les systèmes d'éveil et l'activité électrique spontanée

Les potentiels évoqués par SMT et l'activité électrique spontanée ont été enregistrés durant une session « yeux fermés » (sommeil) et une session « yeux ouverts » (éveil) chez un patient en état d'éveil non-répondant et chez un patient en état de conscience minimale. Lors de la session « yeux fermés », les deux patients présentaient une onde d'activation simple et locale, similaire à celle observée chez les sujets sains endormis ou anesthésiés. Lors de la session « yeux ouverts », le patient en état de conscience minimale a récupéré une réponse corticale étendue et complexe alors que le patient en état d'éveil non-répondant présentait la même réponse simple (figure 14a). Chez les deux patients, l'EEG spontané montrait une

augmentation des fréquences rapides lors de la session « yeux ouverts » par rapport à la session « yeux fermés » (figure 14b). Les mécanismes de connectivité corticale semblent donc dissociés des mécanismes d'éveil (évalués au niveau du comportement et au niveau de l'activité électrique spontanée) puisque le patient en état d'éveil non-répondant présentait la même réponse simple à la suite à de la SMT qu'il ait les yeux ouverts ou fermés.

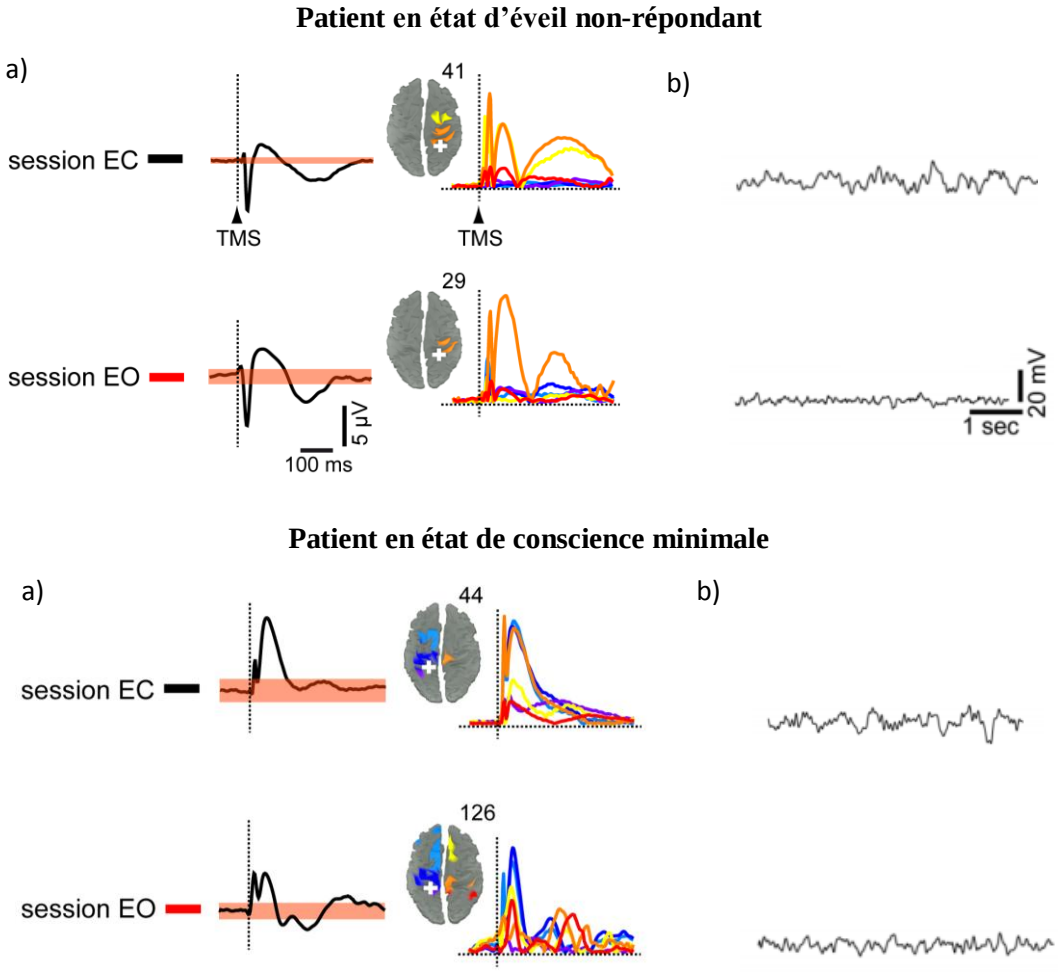


Figure 14. Illustration de la différence entre les mécanismes de connectivité effective et d'éveil. a) Réponses produites par la SMT et b) tracés de l'activité électrique spontanée au niveau du cortex pariétal lors d'une condition 'yeux fermés' (session EC) et d'une condition 'yeux ouverts' (session EO) chez un patient en état d'éveil non-répondant et chez un patient en état de conscience minimale (Gosseries & Rosanova *et al.*, 2012).

Nous avons ensuite examiné si les modifications intervenant dans la connectivité effective pouvaient aussi être dissociées des changements dans l'activité électrique spontanée. Au niveau du groupe, les patients en état de conscience minimale présentaient une diminution des oscillations à haute fréquence (bandes α et β), par rapport aux patients en locked-in syndrome et aux patients sortant de l'état de conscience minimale. Aucun changement

systématique de l'activité électrique spontanée n'a cependant pu être détecté entre les patients en état d'éveil non-répondant et ceux en état de conscience minimale, tant au niveau des sujets individuels qu'au niveau du groupe. À l'inverse, comme nous l'avons vu plus haut, un changement nettement perceptible dans la réponse électrique à la SMT a pu être observé entre ces deux états de conscience. Ces résultats suggèrent que la transition de l'état d'éveil non-répondant à l'état de conscience minimale implique une augmentation considérable de la connectivité effective qui n'est pas nécessairement associée à une modification visible de l'activité électrique spontanée.

5.4 Combinaison avec les données IRM et TEP

Nous avons enregistré les réponses SMT-EEG dans des régions corticales préservées et endommagées chez trois patients en état d'éveil non-répondant (3 hommes de 43, 19 et 81 ans). L'IRM et la TEP ont mis en évidence un cortex cérébral globalement non fonctionnel à la suite d'une anoxie chez le premier patient, une lésion traumatique hémisphérique diffuse chez le deuxième patient, et des lésions ischémiques locales chez le dernier patient (figure 15). Après avoir éliminé les facteurs confondants (artefacts électromagnétiques et musculaires, clignements des yeux et potentiels évoqués auditifs), nous avons constaté chez les trois patients une absence de réponse quand la SMT ciblait des aires corticales lésées, alors qu'une réponse locale et stéréotypée typique de l'état d'éveil non-répondant était obtenue en stimulant des régions relativement préservées (figure 15). Il faut donc éviter de stimuler sur des lésions corticales afin de garantir une fiabilité des réponses lors de l'évaluation de patients sévèrement cérébrolésés. De plus, ces résultats démontrent que les potentiels évoqués par SMT reflètent exclusivement les réponses électriques du tissu cortical (sans artefacts biologiques et électromagnétiques). Enfin, il nous semble indispensable de disposer d'un système de neuronavigation et d'images cérébrales individuelles afin d'évaluer adéquatement les patients cérébrolésés, et si de telles informations ne sont pas disponibles, ces mesures devraient être répétées dans différentes régions corticales (Gosseries & Rosanova *et al.*, soumis).

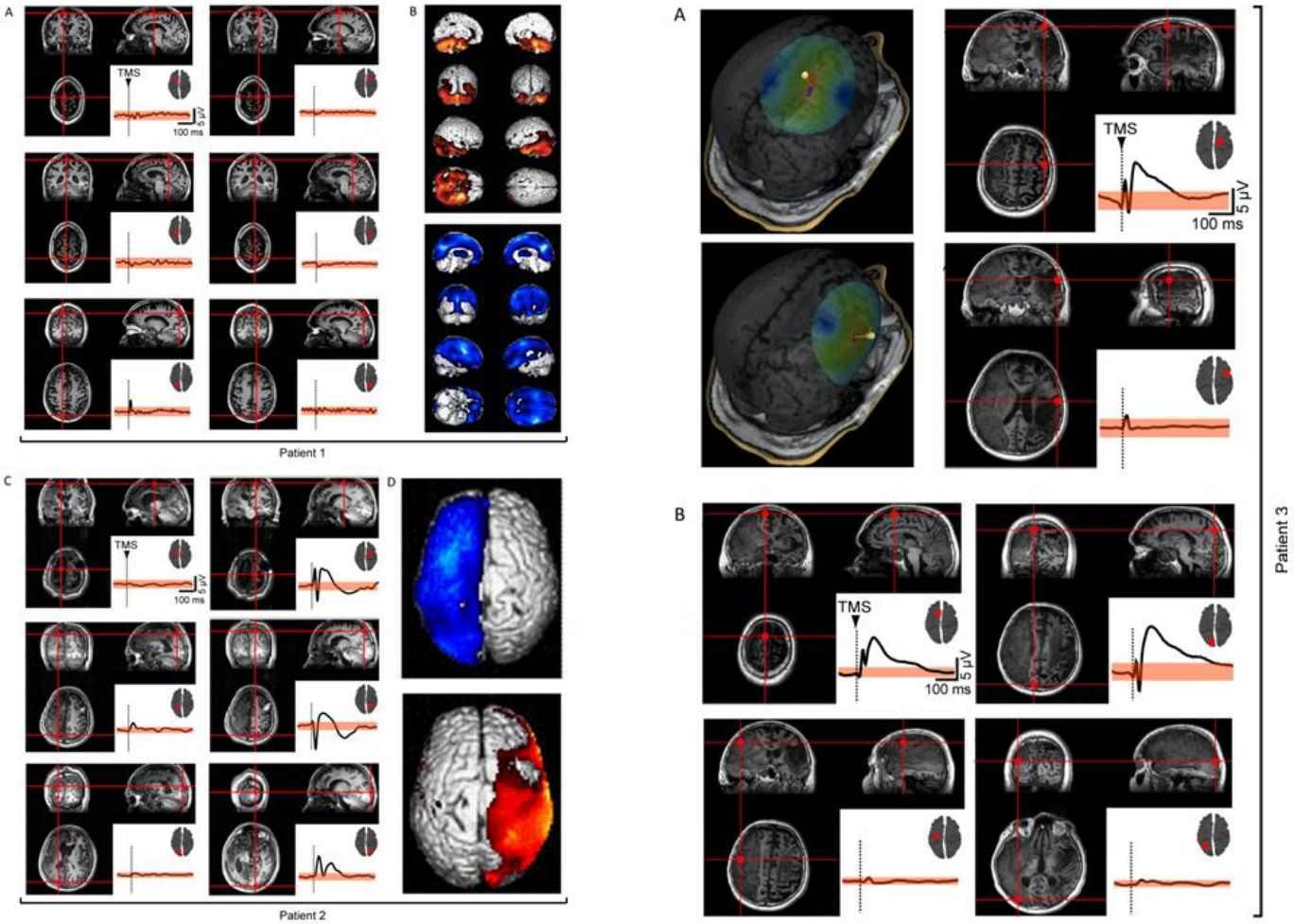


Figure 15. Comparaison des réponses corticales induites par SMT entre des régions cérébrales préservées et endommagées (illustrées par des données IRM et TEP) chez trois patients en état d'éveil non-répondant. Les sites de stimulation sont indiqués par un point rouge. Les images fonctionnelles TEP montrent les régions cérébrales lésées en bleu et les régions relativement préservées en rouge (patients 1&2). Pour le patient 3, les images IRM montrent des anomalies structurelles dans diverses régions cérébrales (Gosseries & Rosanova *et al.*, soumis).

5.5 Conclusion

Dans ce chapitre, nous avons employé la SMT-EEG pour mesurer l'excitabilité corticale et la connectivité corticale effective au chevet de patients en état de conscience altérée. Nous avons montré que, chez les patients en état d'éveil non-répondant, la SMT appliquée au niveau des régions frontales et pariétales n'induisait aucune réponse (dans les cas d'anoxie) ou provoquait une réponse locale et stéréotypée, indiquant une perte de connectivité effective. Ces données confirment à nouveau l'idée que le cerveau de ces patients peut conserver des îlots d'activation (y compris dans les régions associatives), mais que ceux-ci sont déconnectés du reste du cerveau (Schiff *et al.*, 2002; Laureys *et al.*, 2004b). À l'inverse, chez les patients en état de conscience minimale, la SMT déclenchait des réponses électriques

étendues, complexes et de plus longue durée, similaires à celles observées chez les patients en locked-in syndrome et chez les sujets sains éveillés. La technique SMT-EEG permettrait donc d'établir une distinction fiable entre les patients en état d'éveil non-répondant et les patients en état de conscience minimale au niveau individuel (voir groupe I, figure 17). Elle permettrait également de déceler une résurgence de la connectivité corticale effective chez des patients qui récupèrent progressivement une communication fonctionnelle (voir groupe II, figure 17).

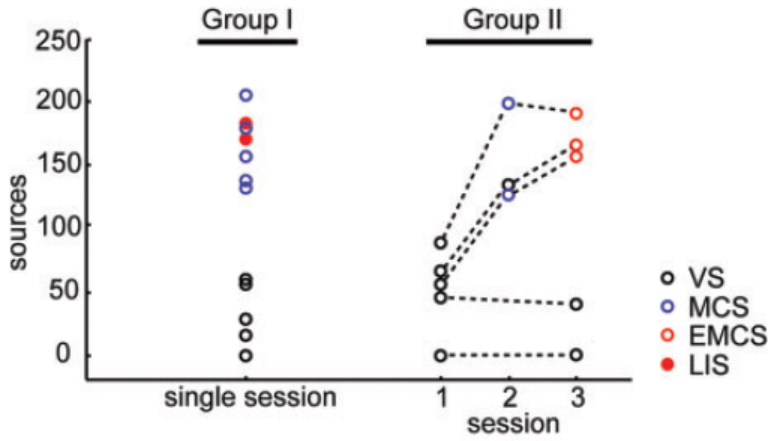


Figure 17. Connectivité cérébrale effective illustrée par le nombre de sources impliquées dans les réponses évoquées chez 17 patients récupérant du coma. Le groupe I représente les patients évalués à une seule reprise et le groupe II représente les patients évalués longitudinalement. La couleur des cercles indique le diagnostic clinique (noir=état d'éveil non-répondant - VS, bleu=état de conscience minimale - MCS, rouge=sortie de l'état de conscience minimale – EMCS, et rouge plein = locked-in syndrome - LIS) (Gosseries & Rosanova *et al.*, 2012).

Nous avons également mis en évidence une dissociation entre les mécanismes d'intégration corticale et les systèmes d'éveil (évalués au niveau comportemental et par EEG). Les systèmes d'activation du tronc cérébral ne semblent donc pas suffisants pour rétablir un niveau minimal de conscience en l'absence de connexions effectives entre les aires cérébrales. En outre, la transition de l'état d'éveil non-répondant à l'état de conscience minimale est détectée par la SMT-EEG, sans modification évidente de l'activité cérébrale spontanée. Enfin, une comparaison avec les données IRM et TEP a démontré une absence de réponse lorsque les régions stimulées étaient endommagées alors que la stimulation des tissus corticaux préservés induisaient des réponses électriques provenant exclusivement du cortex cérébral. Ces derniers résultats soulignent l'importance de disposer d'un système de neuronavigation afin d'éviter de stimuler des aires corticales lésées, ce qui pourrait induire des faux négatifs lors de l'évaluation de la conscience des patients sévèrement cérébrolésés.

D'un point de vue clinique, nos travaux ont montré que la SMT-EEG constitue une nouvelle approche qui permet de détecter les corrélats neuronaux de la récupération de la conscience chez les patients non communicants. Cette méthode peut compléter les protocoles de PE et les paradigmes actifs en IRMf dans la mesure où, contrairement à ces derniers, elle ne dépend pas des capacités du sujet à traiter des stimuli sensoriels, à comprendre ou à suivre des instructions. La SMT-EEG pourrait se révéler particulièrement utile lorsque le diagnostic clinique des patients est ambigu, en apportant un biomarqueur objectif qui servirait à suivre l'évolution des patients et à orienter leur prise en charge. Afin d'optimaliser l'examen SMT-EEG, il faut i) s'assurer que le patient soit bien éveillé, ii) stimuler la face médiane du cerveau en évitant les régions lésées et les sillons corticaux et iii) vérifier l'adéquation de l'intensité de la stimulation. Avant d'implémenter cette technique au chevet des patients en routine clinique, des études sur un plus grand nombre de patients (dans des états cliniques définis et ambigus) sont cependant nécessaires afin de confirmer la validité diagnostique et d'évaluer l'intérêt pronostique de cette technique. Il convient également de mettre au point un dispositif plus simple et une procédure d'analyse des données rapide et standardisée (Massimini *et al.*, 2009). D'autres travaux devraient également être entrepris pour comparer les résultats de la SMT-EEG avec d'autres méthodes neurophysiologiques, comme les PE auditifs (Kotchoubey, 2005; Bekinschtein *et al.*, 2009; Fischer *et al.*, 2010; Boly *et al.*, 2011a) et les enregistrements EEG de longue durée (Landsness & Bruno *et al.*, 2011). Ces mesures conjointes pourraient s'avérer cruciales pour quantifier précisément le potentiel diagnostique (et pronostique) de ces techniques qui peuvent toutes être utilisées au chevet des patients.

D'un point de vue neuroscientifique, la SMT-EEG permet de mesurer directement la capacité des réseaux thalamo-corticaux à interagir entre eux - condition jugée essentielle pour l'émergence de la conscience (Tononi, 2004; Laureys, 2005a; Alkire *et al.*, 2008; Seth *et al.*, 2008; 2008). Les travaux théoriques (Tononi, 2004, Tononi et Koch, 2008), les données expérimentales (Maandag *et al.*, 2007; Alkire *et al.*, 2008; Shulman *et al.*, 2009) et l'observation clinique (Markowitsch et Kessler, 2000; Mataro *et al.*, 2001; Schiff, 2010) indiquent en effet que la conscience dépend de la capacité de régions distribuées du cerveau à interagir par des connexions cortico-corticales et cortico-thalamo-corticales divergentes. Les mesures SMT-EEG de connectivité effective permettent donc de distinguer les états conscients (conscience normale, sommeil paradoxal, état de conscience minimale) des états inconscients (sommeil profond, anesthésie, état d'éveil non-répondant) (Massimini *et al.*, 2005; Ferrarelli *et al.*, 2010; Rosanova *et al.*, 2012). Plus spécifiquement, le fait que la SMT-EEG ait permis de

détecter une différence entre un état d'éveil non-répondant et un état de conscience minimale, mais non entre des niveaux de conscience faible et normal, suggère que la présence d'interactions effectives entre les modules thalamo-corticaux est étroitement corrélée avec la présence d'un niveau minimal de conscience. Enfin, dans le cadre de la présente étude, la SMT-EEG a permis la détection une récupération d'interactions intra-corticales rapides effectives dans le cerveau d'une patiente qui était temporairement retombée dans un état d'éveil non-répondant lors de l'évaluation. Cette dernière observation indique que la connectivité effective corticale se rétablit de façon perceptible avant la récupération d'une communication fiable avec le monde extérieur. On peut en conclure que la connectivité effective entre les modules corticaux semble être un mécanisme neurophysiologique déterminant pour l'émergence de la conscience.

CHAPITRE 6. ASPECTS PSYCHOLOGIQUES LIES A LA PRISE EN CHARGE DES PATIENTS SEVEREMENT CEREBROLESES

« La science ne doit pas être un plaisir égoïste: ceux qui ont la chance de pouvoir se consacrer aux études scientifiques doivent-être aussi les premiers à mettre leurs connaissances au service de l'humanité » (Karl Marx)

Sur base des articles suivants :

Gosseries O, Demertzi A, Ledoux D, Majerus S, Bruno MA, Vanhaudenhuyse A, Chatelle C, Thonnard T, Moonen G , Laureys S, Schnakers C. Needs in families of severely brain-injured patients recovering from coma. *Soumis.*

Gosseries O, Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Thibaut A, Laureys S, Schnakers C. Burnout in caregivers managing chronic patients with disorders of consciousness. *Brain Injury*, accepté.

6.1 Introduction

L'étude des patients récupérant du coma connaît un intérêt croissant avec de nombreuses retombées cliniques, éthiques, légales et scientifiques mais jusqu'à présent, peu d'études se sont portées sur les familles et les soignants s'occupant de ces victimes. Nous avons donc mis un point d'honneur à investiguer les problèmes psychologiques rencontrés par le personnel soignant et les familles lors de la prise en charge de ces patients incapables de communiquer. La prise en charge constitue un véritable défi puisque ces patients présentent d'importants déficits moteurs (ex : spasticité sévère), physiologiques (ex : trachéotomie) et cognitifs (ex : aphasie). La composante émotionnelle est également non négligeable (ex : faible chance de récupération, risque de complications médicales et de décès, conflits entre les soignants et la famille). Pour les familles, d'autres facteurs tels que le sentiment de perte du proche, le changement de statut social et le degré de soutien émotionnel contribuent également aux réactions émotionnelles. Au-delà de la gestion des émotions liées à l'accident du proche, les familles doivent en plus s'approprier les informations médicales fournies par l'équipe soignante, gérer le côté financier de la prise en charge et prendre des décisions sur la vie du proche. L'ensemble de ces facteurs peut avoir un impact sur les relations entre les familles et le personnel soignant (Crawford et Beaumont, 2005) et engendrer une réelle détresse psychologique (Maslach *et al.*, 2001). Un conflit entre la famille et les soignants peut augmenter la détresse que ressentent les deux parties. Il est dès lors crucial de prendre en compte le bien-être du personnel soignant et des familles pour une bonne prise en charge des patients sévèrement handicapés, et ce, en documentant ici le syndrome de burnout chez le personnel soignant et l'importance et la satisfaction des besoins chez les familles.

6.2 Burnout chez le personnel soignant

Le burnout se caractérise par un épuisement émotionnel, une dépersonnalisation (impression de ne plus se reconnaître soi-même, ni la réalité du monde extérieur) et un faible sentiment d'accomplissement personnel. Ce syndrome se manifeste en réponse au stress rencontré dans le milieu professionnel et est relativement fréquent dans les professions visant à s'occuper d'autrui (Maslach *et al.*, 2001). Les secteurs médicaux où le personnel soignant subit à la fois un stress physique et psychologique sont particulièrement touchés, notamment dans les unités de psychiatrie, gériatrie, chirurgie, oncologie, urgence et aux soins intensifs (Chen et McMurray, 2001; Cocco *et al.*, 2003; Sahraian *et al.*, 2008; Trufelli *et al.*, 2008). Le

burnout entraine une diminution de la qualité de vie des professionnels de la santé et produit des symptômes tels que l'anxiété, l'irritabilité, des sautes d'humeur, des insomnies ou encore un sentiment d'échec (Shanafelt *et al.*, 2002; Hyman *et al.*, 2011). Il est également associé à un taux d'absentéisme élevé, une moindre productivité, et constitue un coût important au niveau des soins de santé (Kacenelenbogen *et al.*, 2011). Deux études suggèrent que le stress observé chez les soignants travaillant dans des services de revalidation est lié à la sévérité des lésions du patient ainsi qu'au diagnostic (McLaughlin et Erdman, 1992; Duckett, 1996). Plus récemment, Chiambretto *et al.* ont interrogé 16 personnes travaillant dans une unité prenant en charge des patients en état d'éveil non-répondant. Ils ont montré qu'un niveau d'anxiété et de dépression élevé peut être corrélé à une relation insatisfaisante avec les familles ainsi qu'à la possibilité d'un décès du patient (Chiambretto *et al.*, 2001). Ces études n'ont néanmoins pas investigué la présence d'un burnout au sein du personnel soignant dans ces unités.

Nous avons donc évalué chez le personnel soignant l'impact psychologique de la prise en charge de patients chroniques sévèrement cérébrolésés présentant un trouble de la conscience (Gosseries *et al.*, accepté). Le questionnaire « Maslach Burnout Inventory » (MBI – voir annexe) (Maslach *et al.*, 2001; Cathebras *et al.*, 2004) a été envoyé aux soignants professant dans les 40 institutions spécialisées (centres de neuro-revalidation et maisons de repos) impliquées dans le projet fédéral belge sur la prise en charge des patients en état de conscience altérée (Demotte, 2004). Le MBI est fréquemment utilisé pour évaluer le burnout dans les hôpitaux et se compose de 22 affirmations personnelles (ex., « Je me sens émotionnellement vidé(e) par mon travail ») dont le participant doit estimer la fréquence au niveau professionnel (de jamais à tous les jours). Le MBI explore trois versants: l'épuisement émotionnel, la dépersonnalisation et l'accomplissement personnel. Chaque composante a été divisée en trois niveaux (faible, modéré, élevé) selon les recommandations des auteurs du questionnaire. Le burnout est considéré modéré si le score à l'échelle d'épuisement émotionnel est élevé (>26) ou si le score à l'échelle de dépersonnalisation est élevé (>9). Le burnout est considéré sévère si ces deux composantes sont de niveau élevé (Maslach *et al.*, 2001; Shanafelt *et al.*, 2002; Sahraian *et al.*, 2008). L'accomplissement personnel n'est pas repris dans la mesure du burnout car cette composante n'est pas toujours corrélée négativement avec les deux autres. Les données démographiques suivantes ont également été collectées: l'âge, le genre, le métier (médecin, infirmier/aide soignant, kinésithérapeute/ergothérapeute/logopède ou psychologue/assistant social), l'expérience dans la prise en charge des patients en état de conscience altérée (<4, 4-9 ou >9 ans), le temps passé avec eux (heures par semaine) et le lieu

de travail du participant (centre de neuro-revalidation ou maison de repos). Les analyses ont été effectuées avec STATA (version 11. College Station, TX: StataCorp LP 2009) en utilisant des tests non-paramétriques tels que les tests Chi^2, Kruskal-Wallis et régression logistique (pour plus de détails sur la méthode, voir Gosseries *et al.*, accepté). Les résultats ont été considérés significatifs à $p<0.05$.

Sur 1068 questionnaires envoyés, 568 nous ont été renvoyés (53%). Les analyses ont été effectuées sur 523 participants (exclusion de 45 questionnaires en raison de données manquantes). L'âge moyen des participants était de 37±10 ans (449 femmes) et le temps passé avec les patients récupérant du coma était de 19±14 heures par semaine. Nos résultats ont montré que 18% du personnel soignant interrogé présentaient un burnout, modéré (15%) à sévère (3%), caractérisé par un épuisement émotionnel et/ou une dépersonnalisation sévère(s) (figure 18). Ce résultat suggère qu'une personne sur cinq souffre potentiellement de ce syndrome dans les équipes soignantes s'occupant de patients post-coma. De plus, 33% des participants présentaient un épuisement émotionnel modéré à sévère et 36% une dépersonnalisation modérée à sévère alors que l'accomplissement personnel était considéré comme faible par seulement 3% de notre échantillon. Des résultats similaires ont été trouvés dans certains services d'oncologie et de réanimation (Embriaco *et al.*, 2007; Trufelli *et al.*, 2008).

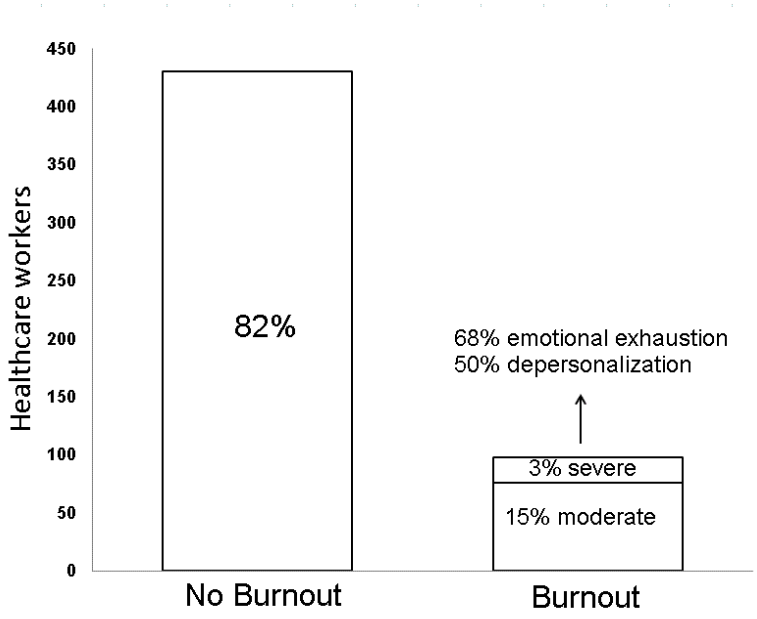


Figure 18. Burnout chez le personnel soignant s'occupant de patients cérébrolésés incapables de communiquer. 18% des participants présentent un burnout modéré (15%) à sévère (3%) caractérisé par une épuisement émotionnel (68%) et/ou une dépersonnalisation (50%) sévères selon le questionnaire « Maslach Burnout Inventory » (Gosseries *et al.*, accepté).

Le burnout semble plus important en fonction du temps passé avec les patients : plus le nombre d'heures par semaine était élevé, plus les participants étaient susceptible de présenter un burnout (23h±14h *versus* 18±14h). Ce facteur avait déjà été observé dans les services de soins intensifs (Embriaco *et al.*, 2007). La proportion de participants présentant un burnout semble également plus importante dans les maisons de repos (23%) que dans les centres de revalidation (14%). Plusieurs raisons pourraient expliquer cette constatation. Le personnel des maisons de repos joue un rôle essentiellement palliatif et doit s'occuper de patients qui se trouvent en phase chronique, qui évoluent lentement et dont le pronostic reste souvent très réservé. Au contraire, dans les centres de revalidation, l'approche est plutôt thérapeutique, les chances d'évolution sont plus probables et les patients y séjournent moins longtemps. En outre, la formation de l'équipe soignante en maison de repos porte principalement sur la prise en charge des patients âgés et non celle de patients sévèrement cérébrolésés. L'équipe médicale se retrouve dès lors impuissante face à une prise en charge qu'elle ne connaît pas ou très peu. Il est néanmoins difficile de savoir si le burnout provient du fait de travailler avec des patients sévèrement cérébrolésés, ou si c'est plus généralement le résultat de s'occuper de personnes âgées. D'autres recherches devraient être réalisées pour répondre à cette question. Des études ont néanmoins montré l'importance du développement des compétences en milieu gériatrique afin d'éviter un épuisement émotionnel (Cocco *et al.*, 2003; Hasson et Arnetz, 2009).

Enfin, notre dernier résultat, et non des moindres, a montré que la profession était la variable la plus associée au burnout ; les infirmiers et les aides soignants étaient plus nombreux à présenter ce syndrome que les autres métiers (24% *versus* 9%). L'équipe infirmière est particulièrement susceptible de développer un burnout vu la nature et la demande émotionnelle de la profession (Sahraian *et al.*, 2008). Plusieurs études ont montré qu'en Belgique, malgré une image positive du métier, la majorité des infirmiers rapporte un travail d'équipe, un support organisationnel et une reconnaissance sociale insuffisants (Milisen *et al.*, 2006; Siebens *et al.*, 2006). Une étude internationale a aussi montré une association entre le burnout du personnel infirmier et l'estimation de la qualité des soins prodigués aux patients (Poghosyan *et al.*, 2010). Le syndrome se développerait souvent suite à une détérioration des relations au sein de l'équipe médicale ou lors de conflits entre les infirmiers et les patients et leurs familles (Sahraian *et al.*, 2008).

6.3 Importance et satisfaction des besoins des familles

Un nombre limité d'études se sont intéressées aux familles de patients récupérant du coma. Après l'annonce d'un grave accident, les proches du patient peuvent ressentir un large panel d'émotions allant du choc à la dépression, en passant par la culpabilité, la dénégation, l'anxiété et l'hostilité envers le personnel soignant (Tzidkiahu *et al.*, 1994). Un tiers des familles de patients ayant subi une sévère lésion cérébrale d'origine traumatique présenterait un niveau important d'anxiété et de dépression, ainsi qu'un pauvre ajustement social (Marsh *et al.*, 2002). Une seule étude s'est intéressée spécifiquement aux familles de patients en état d'éveil non-répondant et a également mis en évidence un niveau d'anxiété et de dépression élevé (Chiambretto et Vanoli, 2006). Cette étude n'a néanmoins évalué que les besoins émotionnels chez ces familles. Nous avons donc évalué l'importance de besoins variés tels que le besoin d'informations médicales, de soutien émotionnel, social, matériel et professionnel ainsi que le besoin d'être impliqué dans les soins administrés au patient (Gosseries *et al.*, soumis).

Le « Family Needs Questionnaire » (FNQ – voir annexe) (Serio *et al.*, 1997) a été envoyé aux familles des patients hospitalisés dans les 40 institutions susmentionnées et à domicile lorsque les patients sont retournés vivre avec leurs proches. Le FNQ est un questionnaire standardisé qui permet d'évaluer les besoins des familles de patients ayant subi une lésion cérébrale (Serio *et al.*, 1997; Murray *et al.*, 2006). Ce questionnaire se compose de 40 affirmations (ex., « J'ai besoin d'être quotidiennement mis au courant de ce qui a été fait auprès du patient ») dont le participant doit estimer l'importance sur une échelle de 1 (pas important) à 4 (très important). Le répondant doit ensuite mentionner si ce besoin a été totalement, partiellement ou pas du tout satisfait. Les données démographiques suivantes ont été demandées: l'âge, le niveau de conscience du patient (coma, état d'éveil non-répondant, état de conscience minimale ou émergence de l'état de conscience minimale), le temps écoulé depuis la lésion cérébrale ainsi que l'âge, le genre du représentant légal et son lien de parenté avec le patient (époux/épouse, père/mère, frère/sœur, fils/fille ou ami/amie). Le lieu d'hospitalisation (centre de neuro-revalidation, maison de repos ou domicile) a également dû être précisé. Les répondants devaient aussi évaluer leur niveau d'anxiété et la fréquence à laquelle ils étaient déprimés. Enfin, ils devaient indiquer leur choix hypothétique concernant une fin de vie pour leur proche. Les analyses ont été réalisées avec STATA (version 11. College Station, TX: StataCorp LP 2009) en utilisant des tests non-paramétriques tels que les

tests Chi^2, Kruskal-Wallis et corrélation de Spearman (pour plus d'information concernant la méthode, voir Gosseries *et al.*, soumis). Les résultats ont été considérés significatifs à $p<0.05$.

Sur 193 questionnaires envoyés, 89 questionnaires valides nous ont été retournés (46%). Les participants (âgés de 51±13 ans, 56 femmes) étaient plus souvent les parents (44%) que les conjoints (29%), les enfants (15%), la fraterie (11%) ou les amis (1%) des patients. Les patients (âgés de 45±16 ans) se trouvaient dans cet état depuis un mois jusqu'à 28 ans et séjournaient dans un centre de revalidation (34%), dans une maison de repos (51%) ou à domicile (15%). Ils étaient considérés en état d'éveil non-répondant (24%), en état de conscience minimale (56%) ou ayant récupéré une communication fonctionnelle (20%). Les besoins d'informations médicales, de soutien social et émotionnel ainsi que l'implication dans les soins ont été considérés comme étant importants par les familles alors que les besoins d'un soutien matériel ou professionnel l'étaient beaucoup moins. Les familles étaient largement insatisfaites pour trois des quatre besoins qu'elles estiment importants (figure 19).

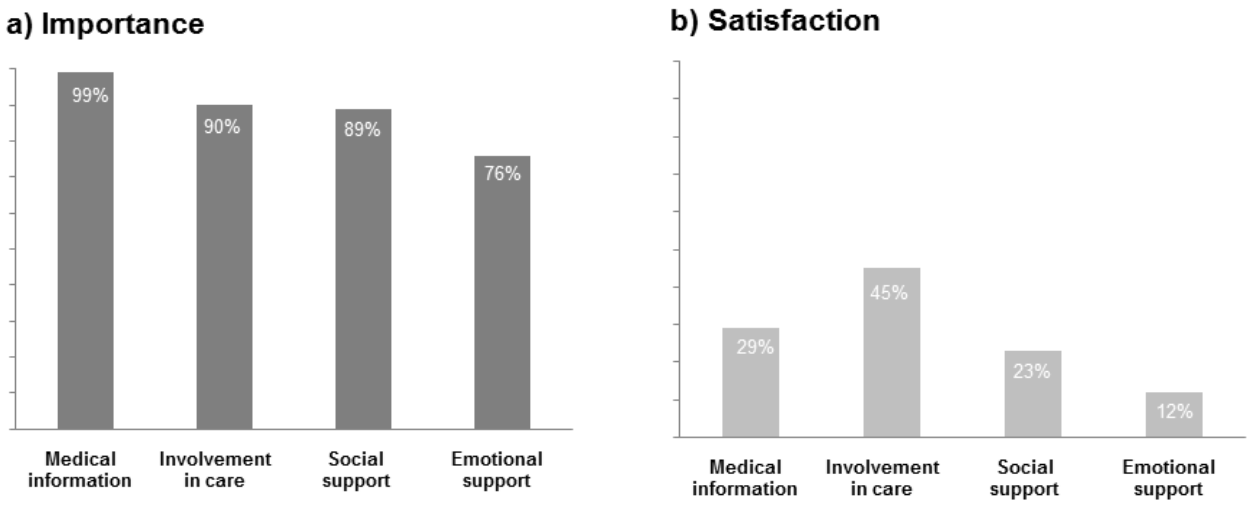


Figure 19. Importance et satisfaction des besoins des familles. a) Les familles rapportent un besoin important d'information médicale, de soutien social et émotionnel et d'implication dans les soins. b) Ces besoins sont largement insatisfaits, surtout au niveau émotionnel (Gosseries *et al.*, soumis).

Le besoin d'information médicale semble être le besoin le plus important pour les familles, et plus particulièrement pour la gent féminine et lorsque les patients sont jeunes. Ce besoin a déjà été rapporté comme étant primordial pour les familles de patients cérébrolésés (Bond *et al.*, 2003; Verhaeghe *et al.*, 2005; 2007). Toutefois, 71% des personnes interrogées déclarent ne pas être satisfaites. Il est donc indispensable de fournir des informations claires et précises afin de réduire le stress et d'améliorer les stratégies d'adaptation des familles (Winstanley *et al.*, 2006). La mauvaise compréhension d'informations médicales est ainsi une

source de conflits les plus communes entre le personnel soignant et les familles. En effet, une mauvaise communication quant à l'espoir à avoir et sur le pronostic du patient peut mener à une hostilité et des plaintes envers le personnel soignant (Tzidkiahu *et al.*, 1994; Verhaeghe *et al.*, 2010).

Le besoin le moins satisfait est le soutien émotionnel (12%), particulièrement chez les personnes plus âgées. Une grande majorité des participants rapportent en outre la présence d'une anxiété (73%) et se sentent déprimés (82%), ce qui a déjà été observé préalablement (McPherson *et al.*, 2000; Marsh *et al.*, 2002; Norup *et al.*, 2010). En outre, seulement 23% des proches sont satisfaits de leur soutien social. Ce problème semble toutefois relativement fréquent puisque plus de 70% des familles prenant en charge des patients en état d'éveil non-répondant déclareraient se sentir isolées socialement et ne s'impliqueraient plus autant dans les activités récréatives (Chiambretto et Vanoli, 2006). Nous avons également observé un lien entre la satisfaction d'un soutien émotionnel et d'un soutien social. Les familles avec peu de support social seraient plus vulnérables émotionnellement (Verhaeghe *et al.*, 2005). De plus, 19% de nos participants souhaiteraient une fin de vie pour leur proche, ceux-là même étaient les moins satisfaits émotionnellement. L'état émotionnel et social peut influer sur le choix des options de limitation de traitements et de fin de vie. Une détection précoce est fondamentale afin de diminuer la souffrance des proches et d'éviter la prise de décisions médicales inadéquates. Les souhaits pour une fin de vie étaient plus nombreux lorsque les patients étaient diagnostiqués en état d'éveil non-répondant (61%). Ce résultat est similaire à ce que nous avons rapporté dans une enquête européenne auprès de professionnels de la santé (n=2475) qui montre que l'arrêt des traitements (c.-à-d. l'hydratation et la nutrition artificielles) est plus souvent considéré lorsque le patient est en état d'éveil non-répondant (66%) que lorsqu'il est en état de conscience minimale (28%) (Demertzi *et al.*, 2011). Si des différences d'opinion apparaissent entre les cliniciens et les familles, il est important que les cliniciens expliquent clairement le statut médical du patient afin de donner l'opportunité aux familles de prendre des décisions adéquates (Kuehlmeyer *et al.*, 2012). Enfin, les désirs de fin de vie étaient aussi plus fréquents lorsque le patient séjournait dans une maison de repos (88%), ce qui peut s'expliquer par la chronicité de l'état médical et les faibles chances de récupération du patient (Hirschberg et Giacino, 2011). En outre, les maisons de repos sont conçues pour accueillir des personnes âgées et le type de soin fourni ne correspond pas toujours aux attentes des parents (Cameron *et al.*, 2001).

6.4 Conclusion

Le syndrome de burnout chez le personnel soignant prenant en charge des patients sévèrement cérébrolésés récupérant du coma est relativement élevé puisqu'une personne sur cinq semble en souffrir, et plus particulièrement les infirmiers et les aides soignants. La prévention du burnout est cruciale puisque celui-ci affecte le bien-être et mène fréquemment à une prise en charge de mauvaise qualité. Plusieurs études mettent en exergue l'importance d'une stratégie d'ajustement efficace (ex : relaxation, approche cognitive, développement des capacités de communication et de résolution de problèmes), d'un soutien social suffisant et d'une structure organisationnelle adaptée afin de maintenir une certaine satisfaction professionnelle et une bonne qualité des soins (Verhaeghe *et al.*, 2005; Dagrada *et al.*, 2011). Des réunions régulières et des sessions de supervision sont donc proposées pour améliorer l'environnement social et la communication au sein des équipes médicales (Kowalski *et al.*, 2010). Détecter des signes de stress chronique tels qu'une charge de travail trop importante ou la présence de conflits relationnels devrait aussi être considéré comme une priorité afin de prévenir le burnout chez le personnel soignant les patients en état de conscience altérée.

Quant aux familles de patients récupérant du coma, prodiguer des informations médicales complètes, précises et simples ainsi qu'un support social et émotionnel suffisant sont les besoins les plus importants mais aussi les moins satisfaits. Les familles rapportent également de l'anxiété et des pensées déprimantes. L'insatisfaction émotionnelle semble aussi plus élevée chez les personnes interrogées qui souhaitent une fin de vie pour leur proche. L'évaluation et la satisfaction de ces besoins sont donc nécessaires afin d'améliorer la qualité de vie des proches du patient mais aussi pour maintenir une bonne relation entre le personnel soignant et les familles et, dès lors, optimaliser la prise en charge du patient. En effet, il n'est pas rare d'observer un burnout parmi le personnel soignant à la suite d'une détérioration des relations avec la famille des patients (Sahraian *et al.*, 2008). Il est donc indispensable de proposer une intervention concrète afin de prévenir une détresse émotionnelle importante (Murray *et al.*, 2006). Des interventions telles qu'une psychothérapie individuelle, des thérapies de groupes (avec d'autres familles vivant des situations similaires), ou des sessions formelles d'informations (pour une meilleure compréhension) sembleraient réduire le stress subi et permettraient aux familles de gérer les problèmes rencontrés de manière plus efficace (Verhaeghe *et al.*, 2005; Chiambretto et Vanoli, 2006). Enfin, il faut souligner que nos résultats peuvent être influencés par un biais de sélection (le taux de réponse étant de ±50%, les répondants sont peut-être ceux qui se sentaient les plus concernés) mais également par un

biais culturel et organisationnel (Demertzi *et al.*, 2011). Des études internationales multicentriques sont nécessaires afin de confirmer nos résultats.

CHAPITRE 7. CONCLUSIONS ET PERSPECTIVES FUTURES

« La science de la réalité ne se contente plus du comment phénoménologique ; elle cherche le pourquoi mathématique » (Gaston Bachelard)

Dans la pratique clinique, poser un diagnostic précis d'état de conscience altérée chez les patients sévèrement cérébrolésés est primordial afin de fournir aux équipes soignantes des indications pronostiques mais aussi pour adapter la prise en charge thérapeutique et prendre des décisions adéquates quant à la revalidation ou la fin de vie. Bien que l'évaluation comportementale est actuellement la méthode de référence pour différencier ces patients, elle aboutit encore trop souvent à des diagnostics erronés. Les techniques paracliniques telles que l'IRM, la TEP et l'EEG permettent de mesurer de manière plus objective l'état de conscience des patients. La sensitivité de ces techniques n'est toutefois pas encore assez satisfaisante pour détecter des signes de conscience au niveau individuel. Le premier objectif de ce travail était de valider de nouveaux marqueurs paracliniques pour optimaliser l'exactitude du diagnostic des patients en état de conscience altérée suite à un coma.

D'un point de vue neuroscientifique, les théories de l'information intégrée (Tononi, 2004), de l'espace de travail neuronal global (Dehaene et al, 2006) et du syndrome de déconnexion (Laureys et al, 2005b) émettent l'hypothèse qu'un réseau neuronal largement connecté et spécialisé est requis pour l'émergence de la conscience. Ces modèles proposent un parallèle entre la connectivité au sein d'un large réseau fronto-pariéto-thalamique et le degré de conscience d'un sujet. Selon la théorie de Tononi (2004), la conscience dépendrait de manière critique de la capacité du cerveau à intégrer l'information, qui est contingente à la connectivité effective entre les aires cérébrales fonctionnellement spécialisées du système thalamo-cortical, et non pas tant du taux de décharge neuronale, ni de la synchronisation dans certaines bandes de fréquence, ou des stimuli sensoriels en soi. En conséquent, la perte de la conscience pourrait être due à une altération de la connectivité effective entrainant une diminution de la complexité cérébrale et un syndrome de déconnexion cérébrale. Le second objectif de notre travail était de tester ces hypothèses neuroscientifiques de la conscience, en intégrant nos résultats dans un cadre théorique général.

Nous avons dans un premier temps testé deux mesures électrophysiologiques cérébrales. La mesure automatisée d'EEG-entropie a permis de discriminer entre les patients inconscients et les patients en état de conscience minimale avec une bonne sensibilité dans les stades aigus (c.-à.-d. moins d'un mois après la lésion cérébrale). La complexité cérébrale mesurée par l'EEG-entropie était corrélée au niveau de conscience des participants, avec une mesure élevée lorsque les sujets étaient (minimalement) conscients et une mesure basse lorsque les patients étaient inconscients. Ces observations confirment une perte de la complexité cérébrale chez ces patients. Cette technique, qui est facilement applicable en

routine clinique, n'a par contre montré aucune valeur pronostique. La deuxième mesure incluait des potentiels évoqués auditifs combinés à des analyses spécifiques de reconstruction de source. Ces données ont démontré une altération des connexions cortico-corticales, et plus particulièrement les connexions rétrogrades fronto-temporales, chez les patients en état d'éveil non-répondant. Ces résultats nécessitent encore une validation au niveau individuel mais confirment néanmoins les hypothèses de la perte de connectivité effective et du syndrome de déconnexion. Une valeur pronostique a également été détectée au niveau du groupe, mais à nouveau, des études longitudinales sur un grand nombre de patients sont indispensables avant d'en tirer des conclusions définitives.

Nous avons dans un second temps utilisé la technique SMT pour mesurer cette fois les connexions cortico-spinales chez nos patients. Les mesures électromyographiques ont montré que les mesures périphériques spinales étaient globalement similaires à celles des sujets contrôles alors que les mesures corticales centrales différaient selon le niveau de conscience. En effet, le seuil moteur, les courbes de recrutement et l'inhibition afférente à courte latence étaient altérés chez les patients, et les deux dernières mesures étaient en lien avec leur niveau de conscience. Ces résultats suggèrent une diminution de l'excitabilité et de l'inhibition cortico-spinale, et un syndrome de déconnexion d'origine corticale.

Enfin, nous avons combiné la SMT à l'EEG afin de mesurer l'effet de la SMT sur l'activité du cortex cérébral et d'évaluer les connexions cortico-corticales. Cette méthode a permis de différencier au niveau individuel les patients en état d'éveil non-répondant des patients en état de conscience minimale. Chez les patients en état d'éveil non-répondant, la réponse était initialement plus forte mais s'éteignait rapidement et ne se dispersait pas au-delà du site de stimulation (comme observé précédemment lors du sommeil profond ou en anesthésie). Pour les cas anoxiques, aucune réponse n'a pu être observée. Chez les patients en état de conscience minimale, une réponse initiale au site de stimulation était suivie par une séquence complexe d'ondes qui se propageaient aux aires corticales adjacentes ipsilatérales et transcalleuses, comme observé chez les patients en locked-in syndrome et chez les sujets sains. Enfin, les patients montrant une récupération progressive de la conscience ont présenté en parallèle une résurgence d'interactions cérébrales rapides et à longue distance. La SMT-EEG est une technique fiable, non invasive et non biaisée par des éléments périphériques confondants. Elle pourrait être utilisée comme marqueur diagnostique de premier choix en routine clinique. Toutefois, des études supplémentaires sont indispensables pour valider ces résultats préliminaires et pour faciliter les procédures d'acquisition et de traitement des

données avant d'implémenter la SMT-EEG en milieu hospitalier. D'autres études sont également nécessaires afin de dégager des facteurs pronostiques chez ces patients. Ces résultats confirment également un syndrome de déconnexion au niveau cortico-cortical et une perte de conscience liée à une altération de la connectivité effective entre les différentes aires cérébrales, et donc à une perte d'intégration et de différentiation de l'activité neuronale (Tononi et Koch, 2008).

Un Index de Complexité Perturbationelle (ICP) a été développé très récemment afin de synthétiser les observations expérimentales obtenues par SMT-EEG dans les différents états de conscience altérée. Cet index mesure la quantité d'informations qui est produite en réponse à la SMT lorsque les différents modules du système thalamo-cortical sont engagés dans des interactions rapides et causales. Ce marqueur s'intègre dans le cadre de la théorie générale de la conscience de Tononi. Bien que l'ICP ne soit pas encore une implémentation directe de la mesure Φ, il est inspiré par la notion d'information intégrée, et évalue la complexité informationnelle (de Lempel-Ziv) des signaux EEG générés en réponse à la SMT. Les valeurs d'ICP seront basses si les interactions causales entre les aires corticales sont diminuées (perte d'intégration) car dans ce cas, l'activation cérébrale suite à la SMT reste localisée. Les valeurs seront également basses si les régions cérébrales interagissent après la perturbation par SMT mais le font de manière stéréotypée (perte d'information). L'ICP sera par contre élevé si la perturbation initiale est transmise à un large nombre de régions intégrées qui réagissent différemment. Comme montré dans la figure 20, les réponses à la SMT correspondent systématiquement à des valeurs d'ICP élevées en état de conscience normale (éveil normal, locked-in syndrome) et à des valeurs basses lorsque le niveau de conscience est réduit (sommeil lent profond, anesthésie générale, état d'éveil non-répondant). Les patients récupérant de l'état d'éveil non-répondant présentaient quant à eux des valeurs intermédiaires. L'ICP semble représenter une mesure globale de la complexité cérébrale reflétant le niveau de conscience observé dans les différents états de conscience.

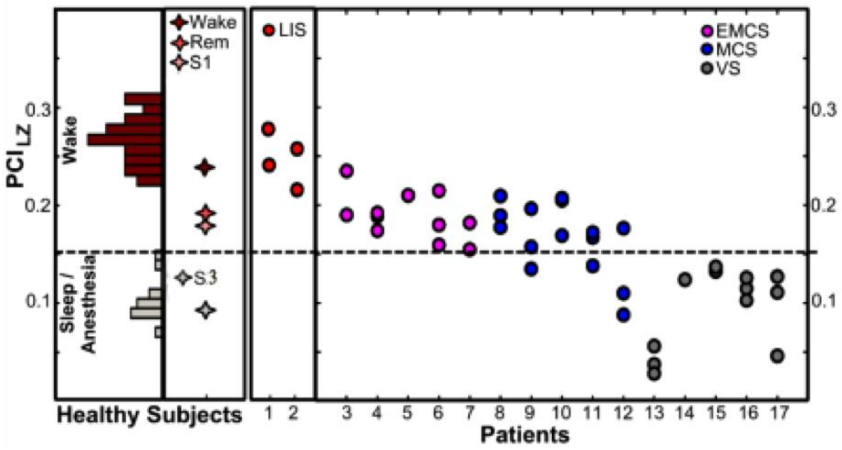


Figure 20. Index de Complexité Perturbationnelle (PCI) calculé dans différents états de conscience. Les valeurs sont élevées chez les sujets sains en éveil normal (wake) et chez les patients en locked-in syndrome (LIS) alors que les valeurs sont basses lors du sommeil profond (sleep S3), en anesthésie et en état d'éveil non-répondant (VS). Les patients récupérant de l'état d'éveil non répondant présentent des valeurs intermédiaires (MCS et EMCS) (Casali, 2011).

Parallèlement à ces résultats, nous avons également montré que la majorité des patients en état de conscience altérée montre des signes de récupération pendant leur séjour en centre de réadaptation. Le statut fonctionnel à l'admission, la durée écoulée depuis l'admission et l'étiologie semblent être des facteurs prédictifs d'une récupération. La prise en charge de ces patients reste toutefois particulièrement lourde pour le personnel soignant et les proches. Les membres des équipes soignantes sont potentiellement à risque de développer un syndrome de burnout, surtout s'ils font partie de l'équipe infirmière, s'ils travaillent dans une maison de repos et si le temps passé avec ces patients est élevé. Les familles des patients peuvent également présenter de graves troubles psychologiques et se sentir déprimés face aux responsabilités concernant les décisions à prendre pour leur proche malade. Il est dès lors indispensable de prendre ces aspects en compte afin d'améliorer la qualité de vie de ces intervenants, en fournissant notamment un support psychologique et social adaptés. Des informations médicales complètes, précises et simples devraient également être fournies aux familles, et ce, pour contribuer à une bonne entente avec le personnel soignant et pour optimiser la prise en charge des patients récupérant du coma.

Dans les perspectives futures, nous proposons d'une part une approche multimodale longitudinale et d'autre part une approche thérapeutique. La première approche permettra d'évaluer l'évolution de la connectivité cérébrale pendant la récupération de conscience chez les patients sévèrement cérébrolésés au moyen de trois mesures indépendantes : la

connectivité fonctionnelle (IRMf de l'état repos), la connectivité structurelle (imagerie par tenseur de diffusion) et la connectivité effective (SMT-EEG). Selon les études neuropathologiques *post mortem* (Adams *et al.*, 2000) et *in vivo* (Fernández-Espejo *et al.*, 2011), les déconnexions cérébrales observées chez les patients en état de conscience altérée sont d'ordre structurel et peuvent être dues en grande partie à des lésions étendues des fibres cortico-corticales ainsi qu'à des lésions thalamiques. En plus des lésions anatomiques, des déficits fonctionnels dans le réseau thalamo-cortical ont également été rapportés, tels que les phénomènes de disfacilitation (Englot *et al.*, 2010), de bistabilité neuronale (Massimini *et al.*, 2009) ou d'une altération de l'équilibre entre les processus d'excitation et d'inhibition (Schiff, 2010). La connectivité fonctionnelle est généralement supportée par la connectivité structurelle, mais elle peut être observée entre des régions qui ne sont pas structurellement connectées, impliquant probablement une connexion indirecte par une troisième région (Damoiseaux et Greicius, 2009). De même, certains patients en état de conscience altérée présentent des déconnexions fonctionnelles dans le réseau du mode par défaut alors que la matrice de substance blanche est préservée (Bruno & Fernández-Espejo *et al.*, 2011). Ces déficits, à la fois structurels et fonctionnels, contribuent probablement à l'altération générale de la connectivité effective observée chez nos patients. Suite à ces constatations, nous proposons de comparer la connectivité effective avec la connectivité structurelle et fonctionnelle afin d'explorer la relation qu'il existe entre ces trois modalités et la récupération de conscience. Dans cette optique, une cohorte de patients en état de conscience altérée sera évaluée entre un et trois mois après l'accident cérébral. Ils seront ensuite réévalués six mois et un an après. Nous intégrerons les résultats des mesures de connectivité fonctionnelle dans les calculs de complexité obtenus par SMT-EEG et nous les modéliserons avec la connectivité structurelle de chaque patient (analyse individuelle). L'intégration des données de connectivité multimodale en un modèle unique pour investiguer la récupération de conscience après un coma nous permettra également d'évaluer le rôle potentiel du précuneus comme région critique dans le 'réseau de la conscience' (Cavanna et Trimble, 2006). En effet, la SMT portera sur le précuneus qui sera préalablement détecté au moyen de l'IRMf et de la DTI. Les connexions entre cette région et d'autres aires cérébrales impliquées dans le réseau de la conscience (ex : cortex préfrontal dorsolatéral, cortex cingulaire) seront ainsi évaluées. Enfin, cette approche permettra également d'investiguer l'intérêt pronostique de ces techniques.

La seconde approche (thérapeutique) consiste à utiliser la SMT-EEG pour évaluer l'efficacité de certains traitements potentiels administrés aux patients récupérant du coma.

Bien qu'aucun traitement ne soit officiellement reconnu pour améliorer le niveau d'éveil et restaurer la conscience chez ces patients, certains traitements ont toutefois induit des effets positifs chez quelques patients (Gosseries *et al.*, 2011c). Les traitements pharmacologiques (amantadine, zolpidem, levodopa, bromocriptine, apomorphine, méthyphénidate, baclofène, sertaline, amitriptyline, désipramine et lamotrigine) et les traitements non-pharmacologiques (réhabilitation physique et cognitive, programmes de stimulation sensorielle, stimulation transcrânienne à courant continu, stimulation cérébrale profonde et SMT répétitive) ont en effet permis des améliorations transitoires ou permanentes chez certains patients en état d'éveil non-répondant et en état de conscience minimale d'étiologies diverses (Gosseries *et al.*, sous presse). Les progrès observés sont variables selon les patients: augmentation de l'éveil, regain de conscience partielle ou totale, amélioration motrice, verbale, cognitive ou encore récupération d'une communication fonctionnelle ou d'une interaction gestuelle. Afin d'investiguer les effets neurophysiologiques qui sous-tendent ces améliorations et de vérifier si l'efficacité de ces traitements passent par la restauration de la connectivité effective au sein du réseau thalamo-cortical, nous proposons dans un premier temps d'évaluer trois traitements que nous connaissons bien dans notre équipe : le zolpidem, l'amantadine et la stimulation transcrânienne à courant continu). Le zolpidem est un agoniste GABA non benzodiazépinergique qui est à la base utilisé comme somnifère mais qui provoque chez certains patients une amélioration rapide (±20min) et transitoire (±4h) du niveau de conscience. Malgré que les mécanismes d'action du zolpidem soient peu connus, ils impliquent probablement l'inhibition du globus pallidus interne (structure inhibitrice du réseau thalamo-cortical) (Schiff, 2010). Nous proposons d'évaluer une dizaine de patients qui répondent à ce médicament au moyen de la SMT avant et après l'administration du traitement (contrôlé par placebo). L'amantadine est un autre agent pharmacologique, principalement dopaminergique, qui est initialement utilisé dans le traitement de la maladie de Parkinson et contre la grippe. Cet agent a induit une accélération de la récupération fonctionnelle chez des patients en état d'éveil non-répondant et en état de conscience minimale dans les stades subaigus (Giacino & Whyte *et al.*, 2012). Comme ces effets mettent plusieurs semaines à s'installer, nous proposons de suivre une dizaine de patients pendant 18 semaines, selon un paradigme ABA et de réaliser plusieurs examens SMT-EEG. Enfin, la stimulation transcrânienne à courant continu a prouvé son efficacité chez les patients atteints de la maladie de Parkinson et plus récemment chez les patients en état de conscience minimale (Thibaut *et al.*, 2011). Les effets bénéfiques observés pourraient s'expliquer par une

augmentation de l'excitabilité des récepteurs NMDA (Nitsche et Paulus, 2000). Nous prévoyons le même type de protocole que pour le zolpidem. Le but final de cette deuxième approche sera d'identifier un mécanisme sous-jacent commun à l'efficacité de ces traitements très différents, qu'ils soient pharmacologiques ou non. Enfin, la SMT répétitive devrait également être investiguée comme traitement potentiel puisque deux études de cas ont rapporté des effets positifs chez un patient en état d'éveil non-répondant (Louise-Bender Pape *et al.*, 2009) et chez un patient en état de conscience minimale (Piccione *et al.*, 2011).

Enfin, l'étude scientifique de la conscience devrait mettre sur un pied d'égalité les mesures neurales et comportementales, sans considérer ces dernières comme référence absolue. Une approche combinant les observations comportementales et les techniques d'évaluations multimodales (ex : TEP, IRM, EEG, SMT-EEG) semble en effet l'approche la plus appropriée pour fournir un diagnostic différentiel de conscience altérée.

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Annexes

Publications scientifiques

Articles

1. Disorders of consciousness: What's in a name?
   Gosseries O*, Bruno MA* (*co-premières), Chatelle C, Vanhaudenhuyse A, Schnakers C, Soddu A et Laureys S.
   NeuroRehabilitation, 28: 3-14, 2011.

2. Assessment of consciousness with electrophysiological and neurological imaging techniques.
   Gosseries O*, Bruno MA* (*co-premières), Ledoux D, Hustinx R, Laureys S.
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3. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients (with supplementary material).
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8. Functional neuroimaging (fMRI, PET and MEG): what do we measure?
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10. Abnormal corticospinal excitability in patients with disorders of consciousness.
    Gosseries O*, Lapitskaya N* (*co-premières), De Pasqua V, Pedersen A, Nielsen JF, Maertens de Noordhout A, Laureys S. *Soumis.*

11. TMS-EEG responses in vegetative state: methodological aspects.
    Gosseries O*, Rosanova M* (*co-premiers), Boly M, Casarotto S, Napolitani M, Schnakers C, Ledoux D, Bruno MA, Massimini M, Laureys S. *Soumis.*

12. Burnout in healthcare workers managing chronic patients with disorders of consciousness
    Gosseries O, Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Thibaut A, Laureys S, Schnakers C. *Brain injury*, accepté.

13. Needs in relatives of patients with disorders of consciousness.
    Gosseries O, Demertzi A, Ledoux D, Majerus S, Bruno MA, Vanhaudenhuyse A, Chatelle C, Thonnard T, Moonen G , Laureys S, Schnakers C. *Soumis.*

Chapitres de livre

14. Disorders of consciousness: coma, vegetative and minimally conscious states.
    Gosseries O, Vanhaudenhuyse A, Bruno MA, Demertzi A, Schnakers C, Boly M, Maudoux A, Moonen G, Laureys S.
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    Gosseries O, Laureys S, Vanhaudenhuyse A.
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    Gosseries O, Bruno MA, Vanhaudenhuyse A, Schnakers S, Laureys S.
    The Neurology of Consciousness. S. Laureys & G. Tononi (Eds.), Elsevier, 191-203, 2009.

17. Pharmacological treatment in patients recovering from coma.
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Questionnaires

1. Maslach Burnout Inventory

2. Family Need Questionnaire

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Disorders of consciousness: What's in a name?

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Abstract. Following a coma, some patients may "awaken" without voluntary interaction or communication with the environment. More than 40 years ago this condition was coined coma vigil or apallic syndrome and later became worldwide known as "persistent vegetative state". About 10 years ago it became clear that some of these patients who failed to recover verbal or non-verbal communication did show some degree of consciousness – a condition called "minimally conscious state". Some authors questioned the usefulness of differentiating unresponsive "vegetative" from minimally conscious patients but subsequent functional neuroimaging studies have since objectively demonstrated differences in residual cerebral processing and hence, we think, conscious awareness. These neuroimaging studies have also demonstrated that a small subset of unresponsive "vegetative" patients may show unambiguous signs of consciousness and command following inaccessible to bedside clinical examination. These findings, together with negative associations intrinsic to the term "vegetative state" as well as the diagnostic errors and their potential effect on the treatment and care for these patients gave rise to the recent proposal for an alternative neutral and more descriptive name: unresponsive wakefulness syndrome. We here give an overview of PET and (functional) MRI studies performed in these challenging patients and stress the need for a separate ICD-9-CM diagnosis code and MEDLINE MeSH entry for "minimally conscious state" as the lack of clear distinction between vegetative state/unresponsive wakefulness syndrome and minimally conscious state may encumber scientific studies in the field of disorders of consciousness.

Keywords: Consciousness, vegetative state/unresponsive wakefulness syndrome, minimally conscious state, functional MRI, positron emission tomography

1. Introduction

Since the invention of the artificial respirator in the 1950s by Bjorn Ibsen in Denmark, many patients who previously did not survive their brain damage and coma now could be artificially ventilated and had their cardiac circulation sustained. This lead to the redefinition of death based on neurological criteria (i.e., brain death) and the notion of therapeutic obstinacy (i.e., the continuation or start of treatment in the absence of any hope of recovery). It also leads to an increased incidence of patients "awakening" from the acute coma while remaining without any sign of voluntary interaction with the environment. Some days to weeks after the acute brain insult (often also after a period of sedation or anesthesia/pharmacological coma) these patients classically open the eyes, start to breath unaided and show spontaneous or stimulus-induced "reflex" or "automatic" movements. This condition was initially named apallic syndrome [46] or coma vigil [21] and in 1972 was coined "persistent vegetative state (PVS)" [43] a

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term now also called "unresponsive wakefulness syndrome" (UWS) [55]. We here discuss the diagnostic challenges encountered in patients with disorders of consciousness (DOC) and the lessons learned from positron emission tomography (PET) and magnetic resonance imaging (MRI) studies in "resting state", *passive* sensory stimulation and *active* "command following" and "communication" paradigms.

2. A rose by any other name would smell as sweet

The name vegetative state (VS) was chosen to refer to the preserved vegetative nervous functioning, meaning these patients have (variably) preserved sleep-wake cycles, respiration, digestion or thermoregulation. The term "persistent" was added to denote that the condition remained for at least one month after insult. In 1994, the Multi-Society Task Force on PVS defined the temporal criteria for irreversibility (that is, more than one year for traumatic and three months for non-traumatic (anoxic) etiology) and introduced the notion of permanent vegetative state [102]. It is to these latter cases that often ethical and legal end-of-life issues, of withholding and withdrawal of life sustaining treatment (that is, artificial hydration and nutrition), are related [23,42]. Unfortunately the abbreviation for Persistent Vegetative State (i.e., PVS) is time and again confounded with the abbreviation for Permanent Vegetative State [49, 56]. In line with the recommendations of the American Congress of Rehabilitation Medicine [1], we prefer to avoid the use of the terms "persistent" and "permanent" in favor of simply specifying the etiology and length of time patients spent in a vegetative/unresponsive condition.

Very recently the European Task Force on Disorders of Consciousness has proposed a more descriptive and neutral term for VS: "Unresponsive Wakefulness Syndrome" (UWS) [55]. "Unresponsive" was chosen to illustrate that these patients only show reflex movements without response to commands. "Wakefulness" refers to the presence of eye opening – spontaneous or stimulation induced – never observed in coma. "Syndrome" stresses that we are assessing a series of clinical signs. Indeed, consciousness is a subjective first person experience and its clinical evaluation is based on the assessment of motor responsiveness. Table 1 shows a list of translations for "unresponsiveness" or UWS permitting medical caregivers an alternative name for "vegetative". The reason for changing the name was mainly justified by the intrinsic negative connotation of the word "vegetative" (unintentionally comparing patients to vegetables) but also by the problems of quantifying consciousness at the bedside (as illustrated by clinical studies assessing possible misdiagnosis) and by neuroimaging studies showing in some (very) rare patients residual cognition inaccessible to behavioral examination. How difficult is it to make the clinical diagnosis of VS/UWS?

Table 1
Translations of unresponsive wakefulness syndrome (UWS), the recently proposed alternative name for "vegetative state" (VS) [55]

Language	Proposed term
English	*unresponsive* wakefulness syndrome
French	syndrome d'éveil *non répondant*
Dutch	*niet responsief* waaksyndroom
German	syndrom des *nicht-responsiven* wachzustandes
Spanish	síndrome de vigilia *sin respuesta*
Italian	sindrome di vigilanza *non responsiva*
Greek	$\sigma\nu\delta\rho o\mu o \quad \mu\eta \quad \alpha\pi o\kappa\rho\sigma\iota\mu\eta\varsigma \quad \varepsilon\gamma\rho\gamma o\rho\sigma\eta\varsigma$
Portuguese	síndrome de vigília *não respondent*
Danish	*uresponsiv* vågenhedsyndrom
Swedish	*oresponsiv* vakenhetsyndrom
Norwegian	*uresponsiv* våkenhetsyndrom

3. Making the bedside diagnosis

Clinical studies conducted in the early 1990s have illustrated how challenging it can be to disentangle reflex behavior (characteristic of vegetative/unresponsive patients) from intermittent voluntary behavior (characteristic of minimally conscious patients) – a problem that can potentially lead to diagnostic error in up to 40% of patients [3,24]. A recent study by Schnakers et al has demonstrated that despite the publication of numerous clinical guidelines on the diagnostic criteria of VS [4,85,103], and despite the publication of diagnostic criteria for MCS [36], these high rates of diagnostic error seemingly remain unchanged when the diagnosis is based on unstructured neurological assessment [96]. In our view, the lessons to learn from these studies on "misdiagnosis" of VS/UWS illustrate the need for standardized "consciousness-scales". It has indeed been shown that the use of validated scales such as the Coma Recovery Scale – Revised (CRS-R) [38] or the Sensory Modality Assessment and Rehabilitation Technique (SMART) [39] permit to identify small, fluctuating and often easily exhaustible motor signs of conscious awareness that can be missed by unstructured clinical assessment [96], or by using acute "coma scales" such as the Glasgow Coma Scale [93] – for review see [2].

Scales like the CRS-R [38] and SMART [39] offer the advantage to systematically search for signs of non-reflex behavior (e.g., visual pursuit or oriented response to noxious stimulation) and command following in a well-defined manner. Visual pursuit, for example, should be assessed by using a moving mirror, as it has been shown that a substantial number of patients will not show eye tracking of a moving object or person, but will do so when using an auto-referential stimulus such as the own face [109]. Conversely, signs such as visual blinking to threat [107] and visual fixation [20] were recently shown not to necessarily reflect conscious awareness and could hence be compatible with the diagnosis of VS/UWS. Finally, the absence of (behavioral) proof of consciousness is not absolute proof of absence of consciousness [70]. It is important that the evaluations are repeated over time and performed by trained experienced assessors. Confounding factors such as drugs with sedative side effects (e.g., against spasticity or epilepsy) or the presence of infection or other medical complications should be accounted for. This situation is even more problematical when patients have underlying deficits with communication functions, such as aphasia, agnosia or apraxia [18,69]. Hence, some behaviorally unresponsive patients could, despite the best clinical assessment, be underestimated in terms of residual cognition or conscious awareness [52]. Since the venue of functional neuroimaging, this challenging issue can be addressed by directly measuring brain activity at rest and during sensory stimulation in these patients (for review see [54,88, 105]).

4. Measuring the brain "at rest"

Historically, the first reliable studies employed positron emission tomography (PET) quantifying the brain's metabolism in resting conditions by use of 18fluorodeoxyglucose (FDG). These early studies needed more invasive methods (repeated arterial blood sampling) to calculate cerebral metabolic rates for glucose metabolism (expressed in mg of glucose use per 100 gr of brain tissue per minute). As summarized in Table 2A, they showed a global and massive decrease in brain activity in VS/UWS [28,61,67,86,104]. However, the reported decrease in global cortical brain metabolism showed some variability with reductions ranging from 25 to 72% of normal values (obtained in healthy waking volunteers). The advent of more sophisticated and data-driven (i.e., voxel-based) statistical analytical tools next permitted to recognize not only *global* changes in brain function but more detailed *regional* differences in metabolic activity distinctive of VS/UWS.

Early voxel-based comparisons [61,62,68] between patients (i.e., wakeful "unawareness") and age-matched healthy controls (i.e., wakeful awareness) demonstrated that VS/UWS patients systematically showed a metabolic dysfunction in a widespread fronto-parietal network encompassing midline (i.e., anterior cingulate/mesiofrontal and posterior cingulate/precuneus) and lateral (i.e., prefrontal and posterior parietal) associative cortices. As was expected, the relatively preserved areas were confined to subcortical, midbrain and brainstem structures known to be involved in autonomous functions such as sleep-wake cycles, thermoregulation and respiration [50]. Recent studies by our and other groups have confirmed these results [10, 20,44,75,98]. These observations made us postulate that consciousness should not be seen as an emergent property of *whole brain* function but rather critically depends on the functional integrity of a neuroanatomically widespread but well-defined *frontoparietal network* [5, 48]. Subsequent functional neuroimaging studies on conscious perception in healthy volunteers [29,83] as well as data obtained in sleep (for review see [71]) and general anesthesia (for review see [17]) have confirmed this "frontoparietal workspace" hypothesis of consciousness. User-independent "consciousness classifiers" [80] can now use patients' FDG-PET brain scans, automatically assess the functional integrity in the frontoparietal network and calculate a probability of being VS/UWS or conscious but "locked-in" – illustrating the translation of scientific knowledge from the bench to the bedside.

Within this frontoparietal "awareness network" the precuneus/posterior cingulate cortex seems to be a "critical hub" [110,111]. Indeed, this area is the most active in conscious resting conditions [82] and seems the most impaired in altered states of consciousness, differentiating VS/UWS from MCS (for review see [66]). Importantly, recovery from VS/UWS seems to be paralleled by the restoration of metabolic activity in the precuneus/posterior cingulate region [53,62]. Similarly, late recovery from MCS was paralleled by axonal regrowth in this region as measured by MRI diffusion tensor imaging [112]. However, we should not make the mistake to reduce a cognitive function to a brain area or network. In addition to the (neophrenological) concept of cerebral functional segregation we stress the importance of functional integration or connectivity.

Table 2
"Resting state" brain function as measured by (A) positron emission tomography (PET) 18fluorodeoxyglucose (FDG) and (B) functional magnetic resonance imaging (fMRI) in disorders of consciousness

Reference	N	Diagnosis	Etiology	Duration	Main findings
A. PET					
Levy et al., 1987 [67]	7	VS/UWS	TBI/NTBI	1–72 m	60% (53–67%) decrease in metabolism
De Volder et al., 1990 [28]	7	VS/UWS	NTBI	1–4 m	53% (43–65%) decrease in metabolism
Tommasino et al., 1995 [104]	10	VS/UWS	TBI/NTBI	2–24 m	56% decrease in metabolism
Rudolf et al., 1999 [86]	24	VS/UWS	NTBI	$<$ 1 m–6 m	25% decrease in metabolism (17% $<$ 3 m and 33% $>$ 3 m)
Laureys et al., 1999 [62]	1	VS/UWS	NTBI	1 m	38% decrease in metabolism; recovery of consciousness = FP recovery
Laureys et al., 1999 [61]	4	VS/UWS	TBI/ NTBI	$<$ 1 m–60 m	FP hypometabolism & disconnections
Laureys et al., 2000 [59]	1	VS/UWS	NTBI	4 m	recovery of consciousness = thalamocortical reconnections
Rudolf et al., 2000 [87]	9	VS/UWS	NTBI	$<$ 1 m	decrease in benzodiazepine receptor density
Laureys et al., 2002 [50]	30	VS/UWS	TBI/ NTBI	1–5 m	56% (37–72%) decrease in metabolism
Beuthien-Baumann, 2003 [10]	16	VS/UWS	TBI	2–12 m	58% decrease in metabolism; FP hypometabolism
Tengvar, 2004 [101]	1	MCS	NTBI	6 m	47–65% FP hypometabolism
Juengling et al., 2005 [44]	5	VS/UWS	NTBI	1–48 m	FP and thalamus hypometabolism
Nakayama et al., 2006 [75]	30	17 VS/UWS 13 MCS	TBI	6–60 m	FP and thalamus hypometabolism in VS/UWS, less impaired in MCS
Silva et al., 2010 [98]	10	VS/UWS	TBI/ NTBI	2–24 m	FP hypometabolism
Lull et al., 2010 [68]	17	VS/UWS & MCS	TBI	12 m	thalamus hypometabolism
Bruno et al., 2010 [20]	10	VS/UWS	NTBI	3 m	FP hypometabolism (VS/UWS without fixation = "MCS" with fixation)
B. fMRI					
Boly et al., 2009 [16]	1	VS/UWS	NTBI	36 m	FP disconnections
Cauda et al., 2009 [22]	3	VS/UWS	TBI/NTBI	20 m	FP disconnections
Vanhaudenhuyse et al., 2009 [108]	13	4 VS/UWS & 5 coma 4 MCS	TBI/NTBI	$<1-60$ m	FP disconnections correlate with consciousness level

Note. N = Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; FP = frontoparietal associative network; TBI = traumatic brain injury; NTBI = non traumatic brain injury; m = months.

Functional connectivity PET studies (acquired at rest and during external auditory and somatosensory stimulation) made us propose to consider VS/UWS as a cortico-cortical [57,60,61] and thalamo-cortical [58, 59] disconnection syndrome. The study of VS/UWS patients who subsequently recovered offered an additional causal link between consciousness and the functional integrity of this frontoparietal network and its long-range cortico-thalamo-cortical connectivity – especially its non-specific (central intralaminar) thalamic projections [59]. The critical role of these diffusely projecting thalamic nuclei in consciousness was corroborated by Schiff et al. [89] deep-brain stimulation study in MCS.

Only recently it became possible to measure "resting state" brain activity by means of non-ionizing functional MRI (fMRI). In contrast to FDG-PET where *one* image is obtained representing the average metabolic activity of approximately 30 minutes, fMRI resting state acquisitions offer a series of scans (i.e., a *time series*) classically obtained during about 10 minutes representing a more indirect measurement of neural function (i.e., assessing hemodynamic changes). These fMRI data obtained at "rest" (that is without any stimulation in contrast to classical fMRI activation studies discussed below) permit to extract (using a multitude of novel and methodologically complicated preprocessing and analyses tools) [99] the so-called "default mode network" activity [15]. This "default mode network", encompassing midline cortices (i.e., anterior cingulate/mesiofrontal and posterior cingulate/precuneus) is thought to reflect internal or self-awareness (i.e., spontaneous thoughts, inner speech and mind wandering) [64,99,106]. Resting state fMRI studies have shown that this network disappears in brain death [16] and decreases in VS/UWS [16,22,108] (Table 2B). MCS patients showed an intermediate pattern with a higher functional connectivity of the posterior cingulate/precuneus area as compared to unresponsive patients [108] – confirming the above-discussed FDG-PET results. Interestingly, the authors also showed a linear correlation between behavioral CRS-R total scores and "default mode network" connectivity.

5. "Activation" studies using sensory stimulation

In the late 1990s functional neuroimaging *activation* studies used ^{15}O labeled water PET measuring regional increases in cerebral blood flow in response to passive external (auditory, somatosensory or visual) stimulation. Table 3A summarizes these studies, showing that for most VS/UWS patients a "low level" cortical activation was reported encompassing primary auditory [13,57,78,90], somatosensory [14,60] or visual [37, 72] cortices. These results showed that sensory stimulation in VS/UWS induced not only subcortical neural activation but also robustly activated gray matter regions [45]. Functional connectivity studies, however, showed that these cortical activations existed like an island isolated from the frontoparietal network discussed above, thought to be necessary for the emergence of conscious perception [11].

The preservation of isolated "low-level" cortical activation to passive sensory stimulation has lately been corroborated by fMRI [9,26,34,41,84] (Table 3B). Moreover, these studies are also showing the potential prognostic value of the technique [25,31]. Indeed, VS/UWS with absent or low-level brain activation (i.e., the majority of the studied cases) have lower chances of subsequent recovery as compared to those with higher-level activation (i.e., activation extending to associative multimodal cortices). The latter pattern of activation is often (albeit not always) encountered in MCS patients [113]. Connectivity studies showed not only a higher level of functional segregation (i.e., more widespread activation) in MCS but also of functional integration (i.e., more functional long range cortico-cortical connectivity with the frontoparietal "awareness" network) as compared to VS/UWS for both auditory [13] and noxious processing [14]. The latter study, showing good evidence of residual pain perception in MCS has obvious clinical consequences.

As for consciousness, pain is a first person subjective experience that cannot be reduced to activity in a single brain region but involves the so-called "pain matrix" [97]. The observed activation of the whole of the pain matrix in MCS [14], including the anterior cingulate and insular areas thought to be important in the affective emotional perception of pain [47] should prompt physicians to systematically use pain killers in MCS, even if (by definition) they cannot communicate their sensations [30]. A recently proposed "pain scale" specifically developed for use in DOC now permits to monitor and adapt the level of nociception/pain and analgesia treatment [92]. This *Nociception Coma Scale* proposes that when the total score (based on assessment of motor, verbal, visual and facial responses) is above 7 out of 12, treatment should be started or continued.

Functional neuroimaging studies have also aimed to address the question whether DOC patients perceive emotions. A series of studies have illustrated that intense or emotionally relevant stimuli induce higher-level activation in MCS (for review [52]). In the auditory modality, these studies have used presentation of meaningful stories told by a relative [7,91] or auto-referential stimuli such as the patient's own name [32,65,81]. The latter studies, for example, show activation of midline structures (i.e., anterior cingulate/mesiofrontal and posterior cingulate/precuneus) [65,81] known to be involved in self-consciousness [64]. However, it should again be stressed that activation of a brain area (or network) per se does not consist an absolute proof of consciousness but could be considered as "automatic" processing.

6. Proving consciousness without movement

In addition to the above reviewed "resting state" and "passive stimulation" functional neuroimaging studies, recent fMRI paradigms aimed at showing proof of command following in the scanner. Mental imagery tasks (such as imagine playing tennis) will activate specific brain areas (premotor cortex for motor imagery) that can easily be picked-up by block-design fMRI [12]. When a behaviorally unresponsive patient repeatedly shows robust activation of premotor cortex if and only if she or he is requested to do the mental imagery task, this constitutes objective evidence that the patient understood and obeyed the command and hence must be conscious. In 2006, this approach first illustrated its potential to show fMRI signs of consciousness unavailable to clinical assessment [76]. The technique was soon adapted to electroencephalography based event related potential (ERP) paradigms and have since proven their utility in clinical routine. In this ERP version of the "imaging playing tennis" fMRI approach, patients were asked to "count a name" leading to a P3 wave on the EEG recording. In the reported series, 21% (3/14) of patients showed ERP proof of command following impossible to demonstrate during repeated behavioral assessments [95]. The technique also permitted to identify a case of complete locked-in syndrome [94]. Similar ERP [6] and electromyographic (EMG) [8] techniques have since been developed showing respectively 20 or 17% of DOC patients demonstrating voluntary

Table 3
Brain activation's level in response to *passive* sensory stimulation as measured by (A) ^{15}O labeled water PET and (B) fMRI in disorders of consciousness

References	Etiology	Duration	N	Diagnostic	Modality	Level of activation
A. PET						
De Jong et al., 1997 [27]	TBI	2 m	1	VS/UWS	auditory (familiar voice)	high
Menon et al., 1998 [72]	NTBI	3 m	1	VS/UWS	visual (familiar face)	low
Schiff et al., 2002 [90]	TBI/NTBI	6–300 m	5	3 VS/UWS	auditory (click), tactile	low
				2 VS/UWS		high
Owen et al., 2002 [78]	TBI/NTBI	4 m	3	1 VS/UWS	visual (familiar face), auditory (noise, words)	low
				2 VS/UWS		high
Laureys et al., 2002 [60]	TBI/NTBI	1 m	15	VS/UWS	pain (electrical stimulation)	low
Kassubek et al., 2003 [45]	NTBI	3–48 m	7	VS/UWS	pain (electrical stimulation)	high
Boly et al., 2004 [13]	TBI/NTBI	1–4 m	20	15 VS/UWS	auditory (click)	low
				5 MCS		high
Laureys et al., 2004 [65]	NTBI	6 m	1	MCS	auditory (noise, cries, own name)	high
Owen et al., 2005 [77]	NTBI	4 m	1	VS/UWS	auditory (speech)	high
Giacino et al., 2006 [37]	TBI/NTBI	1–3 m	5	VS/UWS	visual (flash)	low
Boly et al., 2008 [14]		1–4 m	15	VS/UWS	pain (electrical stimulation)	low
			5	MCS		high
Silva et al., 2010 [98]	TBI/NTBI	2–22 m	10	VS/UWS	tactile	low
B. fMRI						
Moritz et al., 2001 [74]	TBI	$<$ 1 m	1	VS/UWS	tactile, visual (flash), auditory (speech)	high
Bekinschtein et al., 2004 [7]	TBI	5 m	1	MCS	auditory (familiar voice)	high
Bekinschtein et al., 2005 [9]	TBI	2 m	1	VS/UWS	auditory (words)	low
Schiff et al., 2005 [91]	TBI/NTBI	18 m	2	MCS	auditory (speech), tactile	high
Owen et al., 2006 [76]	TBI	6 m	1	VS/UWS	auditory (speech, ambiguity), visual	high
Staffen et al., 2006 [100]	NTBI	10 m	1	VS/UWS	auditory (own name)	high
Di et al., 2007 [32]	TBI/NTBI	2–48 m	11	5 VS/UWS	auditory (familiar voice own name)	low
				2 VS/UWS		high
				4 MCS		high
Coleman et al., 2007 [26]	TBI/NTBI	9–108 m	12	4 VS/UWS	auditory (forward/backward speech, ambiguity)	low
				3 VS/UWS		high
				5 MCS		low/high
Fernandez-Espejo et al., 2008 [34]	TBI	1–11 m	7	2 VS/UWS	auditory (forward/backward speech)	low
				1 VS/UWS		high
				4 MCS		low/high
Rousseau et al., 2008 [84]	NTBI	60 m	4	VS	tactile, visual and auditory	low
Coleman et al., 2009 [25]	TBI/NTBI	2–120 m	46	20 VS/UWS	auditory (forward/backward speech, ambiguity)	low
				7 VS/UWS		high
				19 MCS		low/high
Zhu et al., 2009 [113]	TBI/NTBI	1–2 m	9	MCS	visual (emotional picture)	high
Qin et al., 2010 [81]	TBI/NTBI	2–48 m	11	7 VS/UWS	auditory (familiar voice own name)	low
				4 MCS		high
Fernandez-Espejo et al., 2010 [33]	TBI	1 m	1	VS/UWS	auditory (speech forward/backward)	high
Heelman et al., 2010 [41]	TBI	$<$ 2 m, $>$6 m 14 m	6	6 VS/UWS	visual (flash)	low
				1 MCS		high

Note. N = Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; FP = frontoparietal associative network; TBI = traumatic brain injury; NTBI = non traumatic brain injury; m = months.

response to command inaccessible to clinical bedside examination.

A multicentric fMRI study enrolling 54 patients in Cambridge and Liège similarly showed that in 17% of the cases command following was documented based on neural activity measurements, in the absence of behavioral command following [73]. It should be stressed that these techniques suffer from a low sensitivity (3%), meaning that negative results cannot lead to strong conclusions as many (minimally) conscious brain damaged patients will fail to show command-related fMRI activation. Most interestingly, however, the study showed that fMRI can be used as a way to communicate via yes/no questions. Obviously, EEG based alternatives, called brain computer interfaces or BCIs, that are transportable, cheaper and less sensitive to involuntary movements should now be tested in DOC patients. In our view, the medical community, together with ethi-

Table 4
Current World Health Organization's International Classification of Diseases 2011 ICD-9-CM codes for disorders of consciousness and locked-in syndrome

Diagnosis Code	Diagnosis	Definition
780.0	*Alteration of consciousness*	*None*
−780.01	Coma	Profound state of unconsciousness associated with depressed cerebral activity from which the individual cannot be aroused; coma generally occurs when there is dysfunction or injury involving both cerebral hemispheres or the brain stem.
−780.02	Transient alteration of awareness	None
−780.03	Persistent vegetative state	None
−780.09	Alteration of consciousness other	−Loss of the ability to maintain awareness of self and environment combined with markedly reduced responsiveness to environmental stimuli. −The neurologic status characterized by the occurrence of a loss of the ability to perceive and respond. − Obtundation, a dulled or reduced level of alertness or consciousness.
344.8	*Other specified paralytic syndromes*	
−344.81	Locked-in state	None

Table 5
MEDLINE MeSH Categories for "disorders of consciousness".

Diseases Category
- Nervous System Diseases
  - Central Nervous System Diseases
    - Brain Diseases
      - *Akinetic Mutism*
    - Brain Damage, Chronic
      - *Persistent Vegetative State*
  - Neurologic Manifestations
    - Neurobehavioral Manifestations
      - Consciousness Disorders
        - Unconsciousness
          - *Coma*
          - *Persistent Vegetative State*
- Pathological Conditions, Signs and Symptoms
  - Signs and Symptoms
    - Neurologic Manifestations
      - Neurobehavioral Manifestations
        - Consciousness Disorders
          - Unconsciousness
            - *Coma*
            - *Persistent Vegetative State*

cal and legal scholars [35], needs to prepare the future clinical use and guidelines defining how to make the best possible use of these assisted communication technology in the context of DOC. After we defined when to trust the measurements, we need to define when to consider the patient as competent and capable to express her/his quality of life and to exercise the right of self-determination.

7. Remaining challenges, appropriate indexing and future developments

It is clear that our understanding of consciousness and disorders of consciousness after coma is currently witnessing a paradigm shift, especially thanks to the results obtained in functional neuroimaging [51,79]. The challenge now is to move from single case reports and small cohort reports to large multi-centric studies further addressing the sensitivity and specificity of the discussed "high-tech" para-clinical neuroimaging or electrophysiological tools. In order to propose validated evidence based algorithms specifying when and what investigation needs to be performed in which patient for diagnostic or prognostic purposes, much more research efforts and funding are required. Many of the listed studies were published prior to the formal recognition of the diagnostic criteria of MCS [36], it can hence not be formally excluded that some of these patients might have been minimally conscious. In part of the listed papers, the clinical distinction between, VS/UWS from MCS is suboptimal.

Unfortunately, the World Health Organization does not yet recognize the minimally conscious state in its International Statistical Classification of Diseases (9th Revision, Clinical Modification; ICD-9-CM) diagnosis codes and related Current Procedural Terminology (CPT) medical procedure codes (maintained by the American Medical Association). ICD codes classify symptoms, diseases, or injuries into categories with unique codes permitting standardized epidemiological, morbidity and mortality studies, reimbursement and medical decision-making. The lack of a unique code for MCS hinders comparison with VS/UWS prevalence and prognosis and international statistics (Table 4). We have therefore proposed a 2011 ICD-9-CM Diagnosis Code 780.04 for the minimally conscious state, defined as "non-communicative wakeful patients with inconsistent but clearly discernible behavioral evidence of consciousness to be distinguished from comatose, vegetative or unresponsive patients by the presence of non-reflex movements (e.g., eye-tracking or orientation to pain) or command following".

Likewise, MEDLINE (i.e., Medical Literature Analysis and Retrieval System Online compiled by the United States National Library of Medicine and National Institutes of Health) does not offer a MeSH term (i.e., Medical Subject Heading permitting controlled vocabulary for indexing and database searches) for MCS. At present "MCS" is an entry term included in the MeSH term "Persistent Vegetative State" (introduced in 1995, previously indexed under "Coma"). Note that also locked-in syndrome is not a MeSH entry term whereas MEDLINE indexed "Akinetic Mutism" in 1971 (Table 5).

Undoubtedly, it is an exciting era for the field of brain injury and disorders of consciousness. The gray zones between the different clinical entities in the spectrum following coma are beginning to be better understood and defined by the increasingly powerful neuroimaging technology. As we have here briefly discussed a yet to be determined minority of patients who are currently considered to be "vegetative" or unresponsive, show fMRI or ERP based signs of consciousness that are inaccessible to clinicians' motor-response dependent behavioral assessment. These ever improving technological means are changing the existing clinical boundaries and will permit some "non-communicative" and locked-in [19,40,63] patients to correspond their thoughts and wishes and control their environment via non-motor pathways. In our view, it would be highly preferable to soon have a separate ICD-9-CM Diagnosis Code and MeSH entry for MCS as the lack of clear distinction between VS/UWS and MCS may encumber scientific studies, medical information retrieval, demographic and international analyses in the rapidly changing and challenging field of disorders of consciousness.

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Assessment of consciousness with electrophysiological and neurological imaging techniques

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Purpose of review

Brain MRI (diffusion tensor imaging and spectroscopy) and functional neuroimaging (PET, functional MRI, EEG and evoked potential studies) are changing our understanding of patients with disorders of consciousness encountered after coma such as the 'vegetative' or minimally conscious states.

Recent findings

Increasing evidence from functional neuroimaging and electrophysiology demonstrates some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands, leading to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'.

Summary

Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity. Data from physiological, pharmacological and pathological alterations of consciousness provide evidence in favor of this hypothesis. Increasing our understanding of the neural correlates of consciousness is helping clinicians to do a better job in terms of diagnosis, prognosis and finally treatment and drug development for these severely brain-damaged patients. The current challenge remains to continue translating this research from the bench to the bedside. Only well controlled large multicentric neuroimaging and electrophysiology studies will enable to identify which paraclinical diagnostic or prognostic test is necessary for our routine evidence-based assessment of individuals with disorders of consciousness.

Keywords

consciousness, electroencephalography, functional MRI, minimally conscious state, PET, vegetative state/unresponsive wakefulness syndrome

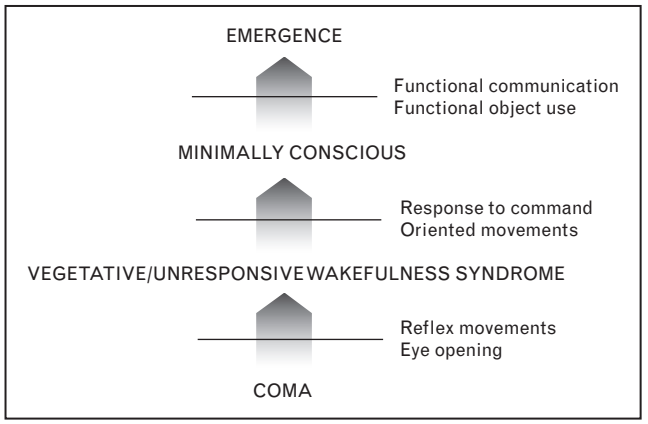
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Introduction

We will here review the medical (i.e. diagnostic, prognostic, and therapeutic) and scientific interest of neuroimaging and electrophysiological studies in disorders of consciousness (DOC) [1•]. Following severe brain damage and coma, some patients may awaken (i.e. open the eyes) but remain unresponsive (i.e. only showing reflex movements). In Europe, this clinical syndrome was initially termed apallic syndrome or coma vigil, but it was later redefined as vegetative state [2]. Since its description more than 35 years ago, an increasing number of functional neuroimaging and event related potential studies (e.g. for recent studies see [3,4]) have shown that it sometimes may be difficult to make strong claims about 'vegetative' patients' awareness [5]. This situation is further complicated when patients have underlying deficits in verbal or nonverbal communication functions, such as aphasia, agnosia or apraxia [6•,7•]. It appears that part of the healthcare, media and lay public continues to feel some unease regarding the unintended denigrating 'vegetable-like' connotation seemingly intrinsic to the term vegetative state. The European Task Force on Disorders of Consciousness therefore recently proposed an alternative name: 'unresponsive wakefulness syndrome' (UWS) [8•]. Hence, physicians are recently offered to refer to these patients as UWS, a more neutral and descriptive term, pertaining to patients showing a number of clinical signs (hence syndrome) of unresponsiveness (i.e. without response to commands or oriented voluntary movements) in the presence of wakefulness. In contrast to coma, which is an acute condition lasting no more than some days or weeks, vegetative state/UWS can be a chronic condition lasting years or

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Figure 1 Clinical criteria of disorders of consciousness



remain permanent. Patients who do recover, classically evolve to a minimally conscious state (MCS), defined by the presence of nonreflex voluntary movements such as orientation to pain, eye tracking or reproducible albeit inconsistent command following. By definition, MCS patients cannot communicate their thoughts or wishes [9]. Finally, in pseudocoma or locked-in syndrome, patients may awaken from coma fully conscious but paralyzed, only able to communicate by eye movements. The medical and ethical management of these vulnerable patients is very complex and a recent article reviewed the even more challenging (but fortunately very rare) situation of locked-in syndrome in children [10•]. Locked-in patients illustrate how difficult it can be to make inferences about subjective conscious awareness in severely motor impaired brain lesioned patients. How can we measure consciousness at the bedside (Fig. 1)?

Quantifying consciousness

The clinical assessment of consciousness relies on disentangling automatic responses from nonreflex-oriented movements or command following. This can be very challenging in coma and related disorders. Motor responses may be very small, inconsistent and easily exhausted, potentially leading to diagnostic errors [11]. A recent prospective study on 103 coma survivors showed that the clinical consensus diagnosis of 'vegetative state/UWS', attributed to 44 patients, was incorrect in 18 cases when properly assessed using a standardized consciousness scale, the Coma Recovery Scale-Revised [12••]. Such a high rate of diagnostic error (i.e. 41%) should prompt clinicians to use validated behavioral scales of consciousness before making the diagnosis of vegetative state/UWS.

Similar to the problem of quantifying consciousness, it remains a clinical and ethical challenge to measure conscious perception of pain in these patients with DOC. A European survey showed that 56% of 1166 medical and 68% of 538 paramedical professionals thought that 'vegetative' patients could feel pain [13•]. Healthcare givers with religious affiliation reported more often that vegetative state/UWS patients might experience pain. Different beliefs on possible pain perception may have consequences in terms of analgesic treatment. When the decision to treat for pain is taken, it remains difficult to monitor the therapeutic effect in these noncommunicative patients. Schnakers *et al.* [14•] therefore proposed a new scale to standardize and evaluate nociception in DOC, the Nociception Coma Scale. When patients score more than 7 on a total score of 12, the authors propose to start analgesia. Objective paraclinical neuroimaging studies are needed to increase our understanding of residual sensation in DOC patients and to propose evidence-based medical guidelines for their care [15•].

Key points

- Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity.
- Electrophysiological and neuroimaging assessments are increasing our understanding of the neural correlates of consciousness and hence permitting to improve diagnosis, prognosis and management of coma and related disorders.
- Recent studies have demonstrated some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands, leading to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'.
- The current challenge remains to continue translating this research from the bench to the bedside offering large controlled multicentric studies to enable identification of evidence-based paraclinical diagnostic and prognostic tests in patients with disorders of consciousness.

Paraclinical diagnostic markers

Structural MRI studies such as diffusion tensor imaging permit to quantify lesions to the brain's white matter tracts, often invisible to conventional radiological approaches [16]. Fernandez-Espejo *et al.* [17•] used this technique in 25 DOC patients of traumatic and nontraumatic cause and showed that vegetative state/UWS could be differentiated from MCS with a 95% accuracy.

Functional imaging such as PET permits to quantify the brain's glucose metabolism in 'resting' (i.e. unstimulated) conditions. Phillips *et al.* [18••] recently developed a

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'relevance vector machine' automated consciousness classifier using metabolic PET scans to categorize, with a 100% accuracy, eight conscious locked-in from 13 unconscious vegetative state/UWS patients. Cerebral PET imaging can also be employed to disentangle reflex from nonreflex movements. Bruno *et al.* [19•] showed that anoxic vegetative state/UWS patients with ($n = 5$) or without ($n = 5$) visual fixation presented an identical brain metabolism and corticocortical functional connectivity, concluding that visual fixation does not necessarily reflect consciousness.

Resting state functional MRI similarly can measure the brain's 'default' activity looking at spontaneous hemodynamic fluctuations in blood-oxygen-level-dependent (BOLD) signal. It has long remained controversial whether these spontaneous fluctuations reflect consciously directed mental activity. However, recent evidence shows that this technique can be used to correlate subjective 'internal' self-related thoughts with activity in midline cortical structures and 'external' sensory perceptions with lateral frontoparietal activity [20]. If this is true, it would be useful to assess fMRI 'resting state' brain fluctuations, considered to reflect spontaneous thoughts, in coma and 'vegetative' patients – who are not supposed to have any thoughts or feelings. Boly *et al.* [21] were the first to use this approach in brain death and vegetative state/UWS, showing a complete absence of 'default mode network' connectivity in the former and a partially preserved activity in the latter condition. Building on these results, Vanhaudenhuyse *et al.* [22••] studied resting-state fMRI connectivity in 14 severely brain-damaged patients of mixed cause, reporting a nonlinear disintegration when conscious locked-in syndrome patients were compared to MCS, vegetative state/UWS and comatose states. Similarly, dysfunctional 'default mode network' connectivity was reported by others in small case series of vegetative state/UWS [23,24], but its diagnostic value at the individual patient level remains to be shown.

fMRI activation studies classically measure the brain's response to external sensory stimuli. Qin *et al.* [25] has studied auditory processing in 11 DOC patients using an autoreferential attention-grabbing stimulus, that is the patient's own name. They reported a linear correlation between activation of the limbic system (anterior cingulate cortex) and the level of consciousness as quantified by the Coma Recovery Scale-Revised. However, such 'passive' stimulation-induced brain activation does permit to make strong claims about the patient's consciousness.

Monti *et al.* [26••] used a so called 'active' paradigm in which patients were instructed to follow simple commands. Their study enrolled 54 DOC cases of different cause in imaging centers in Cambridge and Liège, asking patients to perform two mental imagery tasks: 'imagine playing tennis' (activating motor areas) and 'imagine to walk around in your house' (activating parahippocampal brain regions). Of the 31 patients previously diagnosed as MCS based on standardized behavioral assessments, only one was able to show reliable fMRI activation in the expected brain areas, illustrating that the employed technique only has a sensitivity of 3% in minimally conscious DOC patients (i.e. has a 97% false negative rate). It is more difficult to calculate the technique sensitivity and specificity in vegetative state/UWS patients, as there is no gold standard for assessing consciousness. Indeed, in the published case series, four out of 23 clinically 'unconscious' patients showed fMRI signs of command following and hence of consciousness (i.e. 17%). Nevertheless, given the known low sensitivity, it could be that other patients might have been (minimally) conscious, yet were unable to do the task or show statistically significant brain activation. However, in those individual patients in whom reliable and long-lasting (>30 s) command-related fMRI activation was observed, there seems no other logical alternative explanation other than that they repeatedly understood and replied to the commands and hence truly showed conscious awareness [27,28]. Similarly, a recent study by Rodrigez-Moreno *et al.* [29] used a silent picture-naming task as an 'active' fMRI paradigm searching for proof of consciousness in 10 DOC patients of mixed cause.

In addition to demonstrate proof of consciousness, fMRI can now be used to communicate with some (very exceptional) DOC patients. Indeed, one clinically noncommunicative patient studied in the Liège University Hospital was shown to correctly answer five out of six simple questions regarding his family members' names [26••]. Here, it was set that to communicate 'yes' one should imagine playing tennis (and hence motor area activation was identified using an automated user-independent relative-similarity classifier) and to communicate 'no' the spatial navigation task should be performed (activating parahippocampal areas). fMRI muscle-independent communication currently even goes beyond such yes–no answers to opened questions and is offering the possibility to answer multiple choice questions [30•]. Evidently, these data should be seen as proofs of concept rather than as a practical means to truly assure long-term communication. EEG-based communication devices, called brain–computer interfaces, are therefore being developed as a more practical, transportable and cheaper alternative.

Similarly to the described fMRI 'active' paradigms, EEG-based technology will aim to answer two questions: 'Is the patient conscious?' and, if the answer is affirmative; 'What is that consciousness like?', needing functional communication [31]. The practical utility of demonstrating voluntary brain activity using nonclinical

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means was recently illustrated in the case of a 21-year-old comatose woman who failed to show any motor sign of conscious awareness up to 49 days after an extensive brainstem and thalamic stroke [32]. Only EEG evoked potential based on command following (i.e. counting a target name in a list of names) permitted to make the diagnosis of complete locked-in syndrome shown at the ICU. Similarly, EEG-based evidence of conscious processing (i.e. count a deviant sound sequence in a series of beeps) was demonstrated in three out of four MCS patients while no 'willful' modulation of evoked potentials was recorded in four vegetative state/UWS patients [33]. Ongoing multicentric trials are validating the possible prognostic value of these tests.

Paraclinical tests predicting outcome

Structural MRI diffusion tensor imaging combined with MRI spectroscopy holds promising potential as an objective quantitative outcome-prediction tool [34,35•]. This method provides useful metabolic information on brain damage that may not be visible on classical morphologic imaging. In a cohort of 43 DOC patients studied 2–5 weeks after a traumatic brain injury, the combination of both MRI measurements permitted to predict 1-year unfavorable outcome with up to 86% sensitivity and 97% specificity [36•]. This approach is also being employed in vegetative state/UWS [37] and MCS patients [38]. The prognostic value of MRI spectroscopy was also shown in 90 children with nonaccidental trauma [39•].

The prognostic value of functional MRI 'passive' activation studies was proposed by Di *et al.* [40] concluding that vegetative state/UWS patients with absent or 'low-level' sensory cortex activation showed 100 and 84% of bad outcome, respectively, whereas those showing 'higher-level' associative cortex activation showed a 82% recovery rate (i.e. resulting in a 93% specificity and 69% sensitivity of the included 14 studies encompassing 48 patients). A prospective study using auditory stimulation in 22 vegetative state/UWS and 19 MCS patients recently confirmed the predictive value of fMRI activation studies by demonstrating that the level of cerebral processing correlated with patients' recovery at 6 months follow-up [41•].

Similarly, electrophysiological studies have aimed to predict outcome from DOC. A standardized classification method of routine 'resting-state' EEG showed a correlation at the group level with 3-month outcome measures in 46 DOC patients of varying cause [42]. In a retrospective study of 'resting-state' routine EEG from 50 vegetative state/UWS patients, Babiloni *et al.* [43] showed that increased alpha wave power correlated with 3-month recovery. Cologan *et al.* [44•] recently reviewed the literature on sleep–wake EEG recordings in DOC, discussing the positive predictive value of sleep 'spindle' waves for recovery of consciousness. Using evoked potentials and 'passive' auditory oddball stimuli, the presence of a 'P300' wave to rare stimuli correlated with recovery of consciousness in 34 patients with posttraumatic vegetative state/UWS [45]. Finally, the presence of Pavlovian eye-puff trace conditioning was proposed as a marker of learning in 20 DOC patients, correlating with recovery [46••]. In addition to their clinical diagnostic and prognostic usefulness, these studies have evident neuroscientific importance, helping in our understanding of the neural correlates of human consciousness.

Conclusion

Consciousness can be viewed as the emergent property of the collective behavior of widespread thalamocortical frontoparietal network connectivity [47]. Many of the above-presented studies, and increasing evidence from neuroscientific studies not discussed here on physiological (e.g. sleep [48•,49] and hypnosis [50,51]), pharmacological (e.g. in general anesthesia [52•]) and pathological alterations of consciousness (e.g. [53,54,55•,56•]) provide evidence in favor of this hypothesis. For most neuroscientists, you are your brain. However, such a scientific perspective of human consciousness, awareness or mind is not universally accepted. A recent survey of 782 medical and 290 paramedical professionals showed that more than one-third regarded mind and brain as separate entities. Such dualistic perceptions were predicted most strongly by personal religious and philosophical convictions [57]. The study of consciousness has indeed been the subject of philosophy for centuries. Functional neuroimaging and electrophysiology has now changed this, permitting to make measurements of the brain's activity and correlate this with conscious perception in health and disease. This short review on last year's articles in the field illustrates the increase in our understanding of the neural correlates of consciousness. This knowledge helps clinicians to do a better job in terms of diagnosis [58], prognosis [59] and finally, we hope, treatment [60] and may improve industry drug development (e.g. the use of functional imaging in demonstrating the effect of amantadine [61] and methylphenidate [62] on 'consciousness' networks in DOC patients). Increasing evidence from functional neuroimaging and electrophysiology demonstrates some residual cognitive processing in a subgroup of patients who clinically fail to show any response to commands. This led to the recent proposal of 'unresponsive wakefulness syndrome' as an alternative name for patients previously coined 'vegetative' or 'apallic'. The current challenge remains to continue translating this research from the bench to the bedside – within a well defined ethical framework (e.g. see [63–65]). Only well controlled large multicentric neuroimaging and

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electrophysiology studies will enable to identify which paraclinical diagnostic or prognostic test is necessary, at any given time, for our routine evidence-based assessment of individuals with DOC.

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Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients

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Patients surviving severe brain injury may regain consciousness without recovering their ability to understand, move and communicate. Recently, electrophysiological and neuroimaging approaches, employing simple sensory stimulations or verbal commands, have proven useful in detecting higher order processing and, in some cases, in establishing some degree of communication in brain-injured subjects with severe impairment of motor function. To complement these approaches, it would be useful to develop methods to detect recovery of consciousness in ways that do not depend on the integrity of sensory pathways or on the subject's ability to comprehend or carry out instructions. As suggested by theoretical and experimental work, a key requirement for consciousness is that multiple, specialized cortical areas can engage in rapid causal interactions (effective connectivity). Here, we employ transcranial magnetic stimulation together with high-density electroencephalography to evaluate effective connectivity at the bedside of severely brain injured, non-communicating subjects. In patients in a vegetative state, who were open-eyed, behaviourally awake but unresponsive, transcranial magnetic stimulation triggered a simple, local response indicating a breakdown of effective connectivity, similar to the one previously observed in unconscious sleeping or anaesthetized subjects. In contrast, in minimally conscious patients, who showed fluctuating signs of non-reflexive behaviour, transcranial magnetic stimulation invariably triggered complex activations that sequentially involved distant cortical areas ipsi- and contralateral to the site of stimulation, similar to activations we recorded in locked-in, conscious patients. Longitudinal measurements performed in patients who gradually recovered consciousness revealed that this clear-cut change in effective connectivity could occur at an early stage, before reliable communication was established with the subject and before the spontaneous electroencephalogram showed significant modifications. Measurements of effective connectivity by means of transcranial magnetic stimulation combined with electroencephalography can be performed at the bedside while by-passing subcortical afferent and efferent pathways, and without requiring active participation of subjects or language comprehension; hence, they offer an effective way to detect and track recovery of consciousness in brain-injured patients who are unable to exchange information with the external environment.

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Keywords: coma; TMS; EEG; minimally conscious state; cerebral cortex

Abbreviations: CRS-R = Coma Recovery Scale-Revised; TMS = transcranial magnetic stimulation

Introduction

The level of consciousness of patients who survive severe brain injury is assessed clinically based on their ability to interact with the environment and communicate. Patients who, after careful testing, remain unresponsive to the environment even though their eyes may be open, are considered unconscious or in a vegetative state (Jennett and Plum, 1972; Royal College of Physicians, 1994). The appearance of non-reflexive behaviours, such as visual tracking or responding to simple commands, is considered a sufficient clinical criterion for a minimally conscious state (Giacino *et al.*, 2002, 2004), while functional communication marks the unambiguous emergence of consciousness (emergence from minimally conscious state). As a result of concurrent motor impairments, however, it may happen that brain-injured patients recover consciousness but are unable to signal it behaviourally (Giacino *et al.*, 2009; Schnakers *et al.*, 2009). For this reason, electrophysiological (Kotchoubey *et al.*, 2005; Fellinger *et al.*, 2011) and neuroimaging protocols (Owen *et al.*, 2006; Monti *et al.*, 2010*a*) have been developed to probe for signs of awareness even in patients who are completely unable to move. In these protocols, subjects are instructed with verbal commands to enter and sustain specific mental states (such as imagining to play tennis) while their brain activity is recorded; in this way, a patient can signal that she/he is aware by producing specific neural responses and may, in exceptional cases, establish a basic form of communication (Monti *et al.*, 2010*a*). These mental imagery tasks require high-order cognitive abilities and can be very demanding for many brain-injured subjects; thus, patients in a minimally conscious state (Monti *et al.*, 2010*a*), as well as locked-in patients (Bardin *et al.*, 2011), may fail the test resulting in a significant rate of false negatives. Event-related EEG potentials elicited by simpler sensory (auditory) stimulations, such as P3b, N400, P3a and mismatch negativity, involve lower cognitive resources compared to mental imagery tasks; for example, while the late P3b requires that subjects intentionally pay attention to a target stimulus, the mismatch negativity is an early, automatic reaction to a deviant stimulus that is generated at the pre-attentive level. Although these components can be absent in patients who show behavioural signs of consciousness (Kotchoubey *et al.*, 2005; Fischer *et al.*, 2010; Holler *et al.*, 2011), detecting them in non-responsive subjects is clearly informative. In these particular cases, similarly to functional MRI active paradigms, late event-related EEG potential components, such as P3b, can reveal the recovery of residual cognitive function in patients that are otherwise unresponsive (Schnakers *et al.*, 2008; Faugeras *et al.*, 2011). More generally, event-related EEG potentials allow assessment of the integrity of sensory processing at different hierarchical levels (Kotchoubey *et al.*, 2005; Boly *et al.*, 2011); as such, event-related EEG potentials recorded in the early stages of coma are a good predictor of outcome (Fischer *et al.*, 2004; Daltrozzo *et al.*, 2007; Wijnen *et al.*, 2007; Luaute *et al.*, 2010; Duncan *et al.*, 2011; Faugeras *et al.*, 2011).

In parallel to event-related EEG potential recordings and active paradigms, it would be useful to develop more sensitive methods to detect recovery of consciousness that do not depend on the integrity of sensory and motor pathways nor on the subject's ability to comprehend or carry out instructions. Theoretical considerations (Tononi, 2004; Laureys, 2005; Dehaene *et al.*, 2006; Tononi and Koch, 2008; Seth *et al.*, 2008) as well as experimental data (Del Cul *et al.*, 2007; Alkire *et al.*, 2008) suggest that a basic requirement for consciousness is that multiple, specialized areas of the thalamocortical system can engage in rapid causal interactions (effective connectivity). One way to gauge effective connectivity among thalamocortical modules involves perturbing directly a subset of cortical neurons with transcranial magnetic stimulation (TMS) and recording the reaction of the rest of the brain with millisecond resolution by means of EEG (Ilmoniemi *et al.*, 1997; Litvak *et al.*, 2007; Morishima *et al.*, 2009; Akaishi *et al.*, 2010; Casali *et al.*, 2010). When consciousness is present, the thalamocortical system should respond to TMS with a complex pattern of activation, involving different cortical areas at different times; conversely, it should react with a simple response that remains localized to the stimulated area if consciousness is reduced (Alkire *et al.*, 2008; Massimini *et al.*, 2009*a*). In a recent series of experiments these hypotheses were tested during wakefulness, deep sleep and anaesthesia. In healthy awake subjects, TMS induced a sustained EEG response involving the sequential activation of different brain areas and affecting much of the cortex (Massimini *et al.*, 2005). In contrast, after loss of consciousness induced by general anaesthesia (Ferrarelli *et al.*, 2010), TMS pulses invariably produced a simple response that remained localized to the site of stimulation, indicating a breakdown of effective interactions among thalamocortical modules. A similar breakdown of effective connectivity was observed during slow wave sleep early in the night (Massimini *et al.*, 2005), when subjects report little or no conscious content upon awakening (Hobson *et al.*, 2000). Importantly, during rapid eye movement sleep, when subjects are unresponsive to sensory stimuli and virtually paralysed but report vivid dreams upon awakening, the cortical response to TMS recovered its complexity and became similar to that observed during wakefulness (Massimini *et al.*, 2010).

In the present work we employed TMS/EEG to measure effective connectivity at the bedside of 17 patients who evolved from coma into different clinical states (vegetative state, minimally conscious state, emergence from minimally conscious state and locked-in syndrome). We predicted that measuring effective connectivity should reliably discriminate between patients in a vegetative state and patients in a minimally conscious state with a stable clinical diagnosis (between-subject comparisons) and that a clear-cut resumption of causal interactions should be detectable in the brains of patients who gradually regain consciousness and functional communication (within-subject comparisons).

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Materials and methods

Patients

The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liège. Written informed consents were obtained by the patient's legal surrogates and consents were obtained directly from the patients when they recovered the ability to communicate.

We performed a first set of TMS/EEG experiments (single session) in a group of 12 patients (Group I: five females; mean age ± SD: 50.3 ± 26.21; for more details see Supplementary Table 1). These patients were behaviourally evaluated by means of the Coma Recovery Scale-Revised (CRS-R; Giacino *et al.*, 2004). Evaluation sessions took place four times a week (evaluation week), every other day. These repeated evaluations were carried out in order to avoid diagnostic errors due to fluctuations in responsiveness and to obtain a stable clinical diagnosis. Five patients of Group I (Patients 1–5), showed only reflexive behaviour and were diagnosed as vegetative state during the four behavioural evaluations. Five patients (Patients 6–10) satisfied the CRS-R criteria for minimally conscious state in at least three evaluations, including the one performed on the day of the TMS/EEG session (reported in Supplementary Table 1). The two remaining patients (Patients 11 and 12) could communicate reliably and were diagnosed with locked-in syndrome. The vegetative and minimally conscious state subgroups did not differ systematically in aetiology and time from injury (Supplementary Table 1); in particular, Group I included three chronic patients, one vegetative state (Patient 5: 172 days from injury), one minimally conscious state (Patient 8: 1334 days from injury) and one locked-in syndrome (Patient 12: 1399 days from injury).

A second group of five patients (Group II: three females; mean age ± SD: 51.2 ± 23.05; for more details see Supplementary Table 2) were recruited from intensive care; these patients underwent longitudinal TMS/EEG measurements (Sessions 1–3) as they awakened from coma and progressed towards different clinical states. As assessed by the CRS-R, three of these patients (Patients 13–15) recovered consciousness evolving from a vegetative state, through a minimally conscious state to emergence from minimally conscious state, while two patients (Patients 16 and 17) remained in a vegetative state. Session 1 was performed in all cases, at least 48 h after withdrawal of sedation, when patients exited from coma and entered the vegetative state. In the three subjects (Patients 13–15) who recovered, Session 2 was performed on the day after they transitioned from vegetative to minimally conscious state (however, Patient 15 temporarily slipped back into a vegetative state); in the two patients who did not recover (Patients 16 and 17), Session 2 was performed after 1 month. Session 3 was performed only in the three patients who recovered, after they regained functional communication and emerged from a minimally conscious state (emergence from minimally conscious state).

In summary, we first performed experiments in Group I patients in order to test whether TMS/EEG measures of effective connectivity are able to discriminate between unconscious (vegetative state) and conscious (minimally conscious state, locked-in syndrome) patients with a clear, stable clinical diagnosis (across-subjects comparisons). Then, we recruited Group II patients in order to test, by means of repeated measures, whether changes in effective connectivity are also detectable over time in the brains of individual patients who recover consciousness (within-subjects comparisons).

Transcranial magnetic stimulation targeting and stimulation parameters

A single TMS/EEG session consisted of up to five TMS/EEG measurements that differed either for the site or the intensity of stimulation.

Cortical targets were identified on CT scans acquired with a Siemens Senatom Sensation 16. The TMS stimulator consisted of a Focal Bipulse figure-of-eight coil (mean/outer winding diameter ~50/70 mm, biphasic pulse shape, pulse length ~280 μs, focal area of the stimulation 0.68 cm^2) driven by a Mobile Stimulator Unit (eXimia TMS Stimulator, Nexstim Ltd.). We controlled TMS parameters by means of a Navigated Brain Stimulation system (Nexstim Ltd.) that employed a 3D infrared tracking position sensor unit to locate the relative positions of the coil and subject's head within the reference space of individual CT scan. Navigated brain stimulation also calculated, online, the distribution and the intensity (expressed in V/m) of the intracranial electric field induced by TMS. The location of the maximum electric field induced by TMS on the cortical surface (hot spot) was always kept on the convexity of the targeted gyrus with the induced current perpendicular to its main axis. At least 300 trials were collected for each stimulation site. Stimulation was delivered with an interstimulus interval jittering randomly between 2000 and 2300 ms (0.4–0.5 Hz), at an intensity ranging from 140 V/m up to 200 V/m on the cortical surface; TMS pulses within this range are largely above the threshold (50 V/m) for an EEG response (Komssi *et al.*, 2007; Rosanova *et al.*, 2009; Casali *et al.*, 2010). The CT-guided intracranial electric field estimation was a crucial step during the experimental procedure; due to shifts of intracranial volumes in brain-injured patients, it is difficult to assess whether TMS is on target and effective based on extra-cranial landmarks alone and this may result in false-negatives (absence of EEG response due to missed target or sub-threshold stimulation).

The reproducibility of the stimulation coordinates, within and across sessions (Group II), was guaranteed by a software aiming device that indicated, in real-time, any deviation from the designated target >3 mm. As shown by previous works (Casali *et al.*, 2010; Casarotto *et al.*, 2010), this device ensures high test–retest reproducibility in longitudinal TMS/EEG measurements.

By means of the navigated brain stimulation, TMS was targeted to four cortical sites: the left and right medial third of the superior parietal gyrus and the left and right medial third of the superior frontal gyrus. These cortical targets were selected for the following reasons: (i) they are easily accessible and far from major head or facial muscles whose unwanted activation may affect EEG recordings; (ii) the posterior parietal cortex as well as its interactions with more frontal areas, is thought to be particularly relevant for consciousness (Laureys *et al.*, 2004); and (iii) previous TMS/EEG studies have been successfully performed in these areas during wakefulness (Rosanova *et al.*, 2009), sleep (Massimini *et al.*, 2005, 2007) and anaesthesia (Ferrarelli *et al.*, 2010). In practice, all four cortical sites were not always accessible in all subjects due to skull breaches or external drain derivations. In these cases, TMS/EEG measurements were restricted to two or three cortical sites. In all cases, we avoided stimulating over focal cortical lesions that were clearly visible in CT scans, since the EEG response of these areas may be absent or unreliable.

Electroencephalogram recordings

Both TMS/EEG measurements and spontaneous EEG recordings were performed using a TMS-compatible 60-channel amplifier (Nexstim Ltd). This device prevents amplifier saturation and reduces, or

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abolishes, the magnetic artefacts induced by the coil's discharge (Virtanen *et al.*, 1999). To further optimize TMS compatibility, the impedance at all electrodes was kept $<5\,k\Omega$. EEG signals were referenced to an additional electrode on the forehead, filtered (0.1–500 Hz) and sampled at 1450 Hz. Two extra sensors were used to record the electrooculogram. In the present study, most recordings were free from TMS-induced magnetic or electric artefacts and in all cases the EEG response was artefact-free starting from ~10 ms after stimulation.

Besides the magnetic artefact, other factors may confound the interpretation of TMS-evoked potentials, if not adequately controlled for. For example, TMS may directly stimulate or activate trigeminal sensory afferents and head muscles evoking somatosensory potentials or muscle potentials, respectively. Moreover, the 'click' associated with the coil's discharge propagates through air and bone possibly inducing auditory evoked potentials. In the present experiments, as in previous studies (Massimini *et al.*, 2005; Ferrarelli *et al.*, 2008; Rosanova *et al.*, 2009), we have applied the following procedures in order to eliminate, or control for, these confounding factors. (i) Trigeminal stimulation and muscle artefacts were minimized by placing the coil on a scalp area close to the midline, far away from facial or temporal muscles and nerve endings; (ii) to prevent contamination of TMS-evoked EEG potentials by the auditory response to the coil's 'click', subjects wore earphones through which a noise masking, reproducing the time-varying frequency components of the TMS 'click', was played throughout each TMS/EEG session. Additionally, in two patients, sham stimulation was performed as in previous works (Massimini *et al.*, 2005; Rosanova *et al.*, 2009) and demonstrated the absence of auditory evoked potentials. Noise masking was also effective in preventing TMS from causing blinks or eye muscle reactions; and (iii) bone conduction of the TMS-associated 'click' was minimized by placing a thin foam layer between the coil and the EEG cap. These procedures ensure genuine EEG responses to direct cortical stimulation with TMS. These responses reveal patterns of excitability and connectivity that are specific for the site (Kahkonen *et al.*, 2005*a*; Rosanova *et al.*, 2009; Casali *et al.*, 2010), the angle (Bonato *et al.*, 2006; Casarotto *et al.*, 2010) and the intensity of stimulation (Komssi *et al.*, 2004*b*; Kahkonen *et al.*, 2005*b*; Rosanova *et al.*, 2009). During off-line data processing, all trials that contained spontaneous blinks, eye movement, or muscle artefacts were rejected using an automatic algorithm (Casali *et al.*, 2010). After artefact rejection, 72 good TMS/EEG measurements were further analysed and were included in the present study.

General experimental procedures

During each TMS/EEG session patients were lying on their beds, awake and with their eyes open. If signs of drowsiness appeared, recordings were momentarily interrupted and subjects were stimulated using the CRS-R arousal facilitation protocols. Throughout every recording session the stability of stimulation coordinates was continuously monitored. If the virtual aiming device was signalling a displacement >4 mm, the session was interrupted and the coil was repositioned. At the end of the experiment, the stimulation coordinates were recorded and the electrodes positions were digitized.

Data analysis and statistics

Data analysis was performed using Matlab R2006a (The MathWorks). First, TMS/EEG trials containing noise, muscle activity or eye movements were automatically detected and rejected (Casali *et al.*, 2010). Then, EEG data were average referenced; down-sampled to half of the original sampling rate (725 Hz), band pass filtered (1–80 Hz) and baseline corrected over 300 ms prestimulus. After trials rejection, each TMS-evoked response was obtained by averaging 150–250 artefact-free trials. In order to obtain the overall amount of electrical activity induced by TMS, we calculated the global mean field power (GMFP) (Lehmann and Skrandies, 1980) from the multichannel average signals as follows:

$$GMFP(t) = \sqrt{\frac{\Sigma_i^k (V_i(t) - V_{mean}(t))^2}{k}}$$

where k is the number of channels, V_i is the voltage measured with channel i, and V_{mean} is the mean of the measured voltages across channels (average reference).

Effective connectivity is defined as the effect of the activation of a subset of neurons on other neuronal groups (Friston, 2002). TMS/EEG allows activating directly a subset of cortical neurons and recording the immediate effects of this initial activation in the rest of the brain. Thus, detecting significant TMS-evoked cortical activations (primary neuronal currents) far away from the site of the initial perturbation provides a coarse, but straightforward, indication of effective connectivity (Paus, 2005). In order to detect significant TMS-evoked cortical activations we proceeded as follows. First, we detected primary currents by performing source modelling. Statistical Parametric Mapping software (SPM, freely available at http://www.fil.ion.bpmf.ac.uk/spm) was used to compute cortex, skull and scalp meshes (3004, 2000 and 2000 vertices, respectively) and to co-register these meshes with EEG sensors positions by rigid rotations and translations of anatomical landmarks (nasion, left tragus and right tragus). Conductive head volume was modelled according to the three-spheres BERG method (Berg and Scherg, 1994) as implemented in the Brainstorm software package (http://neuroimage.usc.edu/brainstorm). Finally, the inverse solution was computed on the average of all artefact-free TMS/EEG trials using the minimum norm estimate with smoothness prior, a method that has the advantage of requiring no *a priori* assumption about the nature of the source distribution (Hamalainen and Ilmoniemi, 1994) and of providing stable solutions also in the presence of noise (Silva *et al.*, 2004). Though the minimum norm estimate tends to result in a blurred picture of cortical activation, the location of the maximum estimated current has been shown to reflect the location of the generator of neural activity with good accuracy (<20 mm) (Babiloni *et al.*, 2000; Hauk, 2004; Komssi *et al.*, 2004*a*).

As in previous TMS/EEG works performed during sleep (Massimini *et al.*, 2005, 2007, 2010), we considered only the cortical activations that corresponded to significant GMFP values (see Supplementary Fig. 1 for a graphical example). To assess the threshold for significance (Supplementary Fig. 1), a bootstrap method (Delorme and Makeig, 2004; Lv *et al.*, 2007; McCubbin *et al.*, 2008), which does not assume normal distribution of the observations, was applied by shuffling the time samples of GMFP prestimulus activity (from -300 to -50 ms) at the single-trial level and by calculating 500 surrogated prestimulus GMFP time-series. From each random realization, the maximum value across all latencies was selected to obtain a maximum distribution (control for type I error) and significance level was set at $P < 0.01$. At each significant latency of the post-stimulus GMFP, the location of maximum neuronal current (10 most active sources) was detected on the cortical surface. Plotting and counting the sources involved by maximum neuronal currents across all significant time points in the first 300 ms post-stimulus resulted in the cortical maps and in the values reported in Figs 1–3 and Supplementary Figs 1–3 and 5.

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According to this procedure, the number of detected sources is small if TMS triggers neuronal activations (maximum currents) that remain confined to the stimulated area during the entire post-stimulus period. On the contrary, the number of detected sources is large if TMS triggers maximum cortical currents that involve different cortical areas at different times. In order to describe the time course of TMS-evoked cortical activations in different areas, the currents from a grid of six cortical sources (Fig. 1 and Supplementary Figs 1 and 2) were extracted and auto-scaled to the maximum value of each session. Sources and time series of cortical currents were colour-coded according to their anatomical location in six arbitrary macro-areas.

Spontaneous electroencephalogram recordings and analysis

The spontaneous EEG was recorded immediately before each TMS/EEG session. Similarly to TMS/EEG recordings, EEG recordings were obtained while subjects were behaviourally awake and with their eyes open; if signs of drowsiness appeared, the recordings were momentarily interrupted and patients were stimulated according to the CRS-R arousal facilitation protocol. Hence, all recordings were presumably carried out during a state of high activation of brainstem arousal systems. Continuous EEG acquisitions were split into 5-s epochs. Based on an automatic procedure (Casali *et al.*, 2010), epochs displaying electrooculogram deflections exceeding 70 μV (indicating ocular activity) and/or absolute power of EEG channel F8 in the fast beta range (>25 Hz) exceeding 0.9 μV^2/Hz (indicating activity of fronto-temporal muscles) (van de Velde *et al.*, 1998) were rejected. After epochs rejection the average overall duration of retained epochs was 133.67 s (min: 125 s; max: 170 s). In order to be consistent across subjects, we restricted the analysis to the first 2 min of artefact-free EEG recorded in each patient. Following EEG filtering (1–40 Hz) and channels rejection, Fast Fourier Transform (FFT) was performed and each frequency bin was normalized to total power. The obtained power spectral densities were then subdivided into standard EEG frequency bands (δ, 1–4 Hz; θ, 4–8 Hz; α, 8–12 Hz; and β, 12–25 Hz). At the group level, differences between conditions (vegetative state, minimally conscious state and locked-in syndrome-emergence from minimally conscious state) were tested by performing separately for each frequency band a one-way ANOVA, followed by *post hoc* Bonferroni corrected *t*-test. In the five subjects who underwent longitudinal recording sessions (Group II) and in the two patients recorded both during behavioural sleep and wakefulness, changes in the EEG spectrum were assessed statistically at the individual level by means of a two tailed paired *t*-test.

Results

Using a TMS-compatible 60-channel EEG amplifier we recorded TMS-evoked EEG potentials in 17 patients. In each subject, we performed different stimulation/recording sessions during which we targeted the parietal lobe (superior parietal gyrus) and the frontal lobe (superior frontal gyrus) bilaterally. In total, 72 stimulations were successfully performed and analysed. During all stimulation/recording sessions patients were lying on their beds, awake and with their eyes open.

Measuring cortical effective connectivity allows single subject discrimination between vegetative patients and patients who show some level of consciousness

Building on previous measurements performed in awake, sleeping (Massimini *et al.*, 2005, 2010) and anaesthetized subjects (Ferrarelli *et al.*, 2010), we first tested the ability of TMS/EEG to discriminate between consciousness and unconsciousness in brain-injured patients. A group of 12 patients (Group I) underwent a TMS/EEG session after 1 week of repeated behavioural evaluations by means of the CRS-R (Giacino *et al.*, 2004). Five subjects from this group showed only reflexive behaviour, remained unresponsive to the environment during the whole observation period and were diagnosed in a vegetative state (Supplementary Table 1). As shown in Fig. 1A and Supplementary Fig. 2A, TMS evoked a slow, positive-negative EEG response in all patients in a vegetative state except for one anoxic patient (Patient 4) in whom no response could be elicited even when TMS was delivered at high intensity (200 V/m) in both hemispheres (Supplementary Fig. 2A and 4). The coloured maps show, for each subject, the cortical sources that were involved by TMS-evoked maximum neuronal currents during the significant intervals of the post-stimulus period (0–300 ms) (see 'Materials and methods' section and Supplementary Fig. 1 for details about the statistical procedure). At the right side of each map the number of detected sources is reported together with the time series of neuronal currents recorded from six selected cortical areas (Supplementary Fig. 1). In all patients in a vegetative state, TMS elicited maximum cortical currents that remained localized during the entire significant post-stimulus period, involving a small number of sources around the stimulated area. The stereotypical, local positive-negative wave triggered by TMS in patients in a vegetative state closely resembled the one previously observed during deep sleep (Massimini *et al.*, 2005) and anaesthesia (Ferrarelli *et al.*, 2010), when subjects, if awakened, report little or no conscious experience. Thus, TMS/EEG measurements revealed a substantial impairment of inter-areal causal interactions in the brain of patients who were open-eyed, behaviourally awake but presumably unconscious.

Five subjects of Group I satisfied the CRS-R criteria for a minimally conscious state during the observation period (Supplementary Table 1). These patients showed fluctuating signs of non-reflexive reactions to external stimuli (such as visual pursuit or responses to simple commands) but were unable to communicate reliably with the examiners. In these cases, TMS invariably triggered a complex EEG response associated with a rapidly changing pattern of cortical activation, where maximum neuronal currents shifted over time from the stimulated site to a large number of distant sources (Fig. 1B and Supplementary Fig. 2B). This pattern contrasted starkly with the local, simple wave recorded in patients in a vegetative state and was, instead, comparable to the one obtained in two subjects with locked-in syndrome (Fig. 1C and Supplementary Fig. 2C). Subjects with locked-in syndrome, though being largely paralysed

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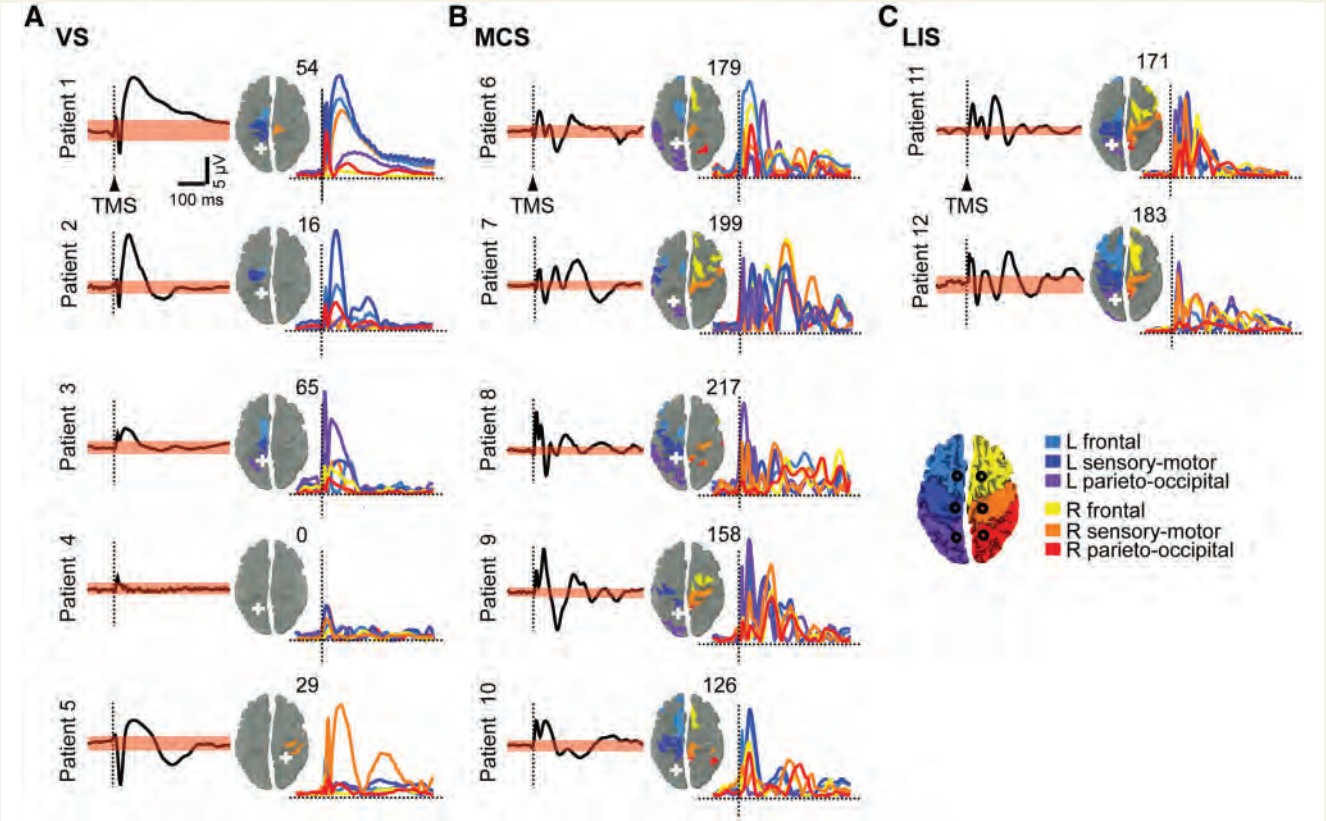


Figure 1 TMS-evoked cortical responses in Group I patients. A group of five vegetative state (VS, **A**), five minimally conscious state (MCS, **B**), and two patients with locked-in syndrome (LIS, **C**) underwent one TMS/EEG session after 7 days of repeated evaluations by means of the CRS-R. For each patient, the averaged TMS-evoked potentials recorded at one electrode under the stimulator (black trace) and the respective significance threshold (upper and lower boundaries of the pink bands; bootstrap statistics, $P < 0.01$) are shown. The sources involved by maximum cortical currents (10 most active sources) during the significant post-stimulus period of the global mean field power are plotted on the cortical surface and colour-coded according to their location in six anatomical macro-areas as indicated in the legend; the number of detected sources is indicated at the *top right* of each map. The time-series (colored traces) represent TMS-evoked cortical currents recorded from an array of six sources (black circles on the cortical map in the legend) located ~2 cm lateral to the midline, one for each macro-area (Supplementary Fig. 1). The white crosses mark the sites of stimulation. For all patients, the responses to the left parietal cortex stimulation are shown, except for one patient (Patient 5) in whom a significant response could only be detected in the right hemisphere (Supplementary Fig. 2). EEG positivity is upward. L = left; R = right.

at the time of recording, could signal that they were fully aware through vertical eye movements. In Fig. 3 the number of sources involved by the propagation of TMS-evoked maximum currents (effective connectivity) is reported for all TMS/EEG sessions (Fig. 3A), all sites of stimulation (Fig. 3B) and all patients; clear-cut differences in cortical effective connectivity discriminate between individual patients in a vegetative state and patients in a minimally conscious state with a stable clinical diagnosis (Group I in Fig. 3A and B).

Cortical effective connectivity recovers in the brain of patients who recover their ability to communicate

If effective connectivity among thalamocortical modules is a key neurophysiological mechanism for some level of consciousness to emerge, then it should clearly recover in the brain of an individual patient before he recovers his ability to communicate reliably. To test this hypothesis we performed longitudinal TMS/EEG measurements in a group of five patients (Group II) who were recruited from the intensive care as soon as they awakened from coma. As assessed by means of the CRS-R (Supplementary Table 2), three of these patients (Fig. 2A and Supplementary Fig. 3A) recovered consciousness and functional communication, evolving from a vegetative state through minimally conscious state to emergence from minimally conscious state, whereas two patients (Fig. 2B and Supplementary Fig. 3B) remained in a vegetative state. In all cases the first TMS/EEG session (Session 1) was performed at least 48 h after withdrawal of sedation, when patients opened their eyes and were diagnosed as in a vegetative state. At this time, similar to the patients in a vegetative state in Group I, TMS evoked a simple wave and a local pattern of activation or no response at all (Patient 17, anoxic) (Fig. 2B, Supplementary Fig. 3B and 4).

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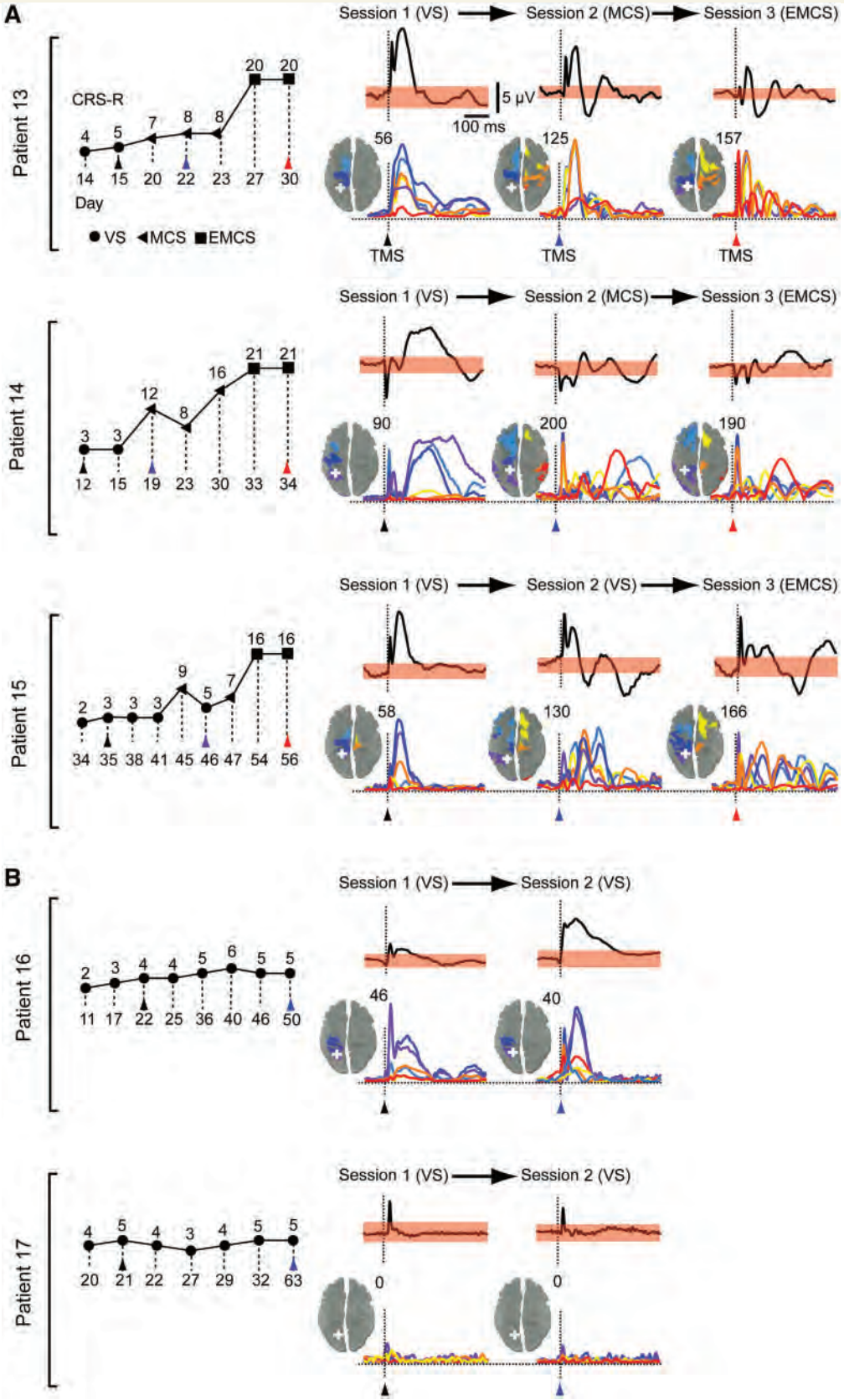


Figure 2 Clinical evaluation and TMS-evoked cortical responses in Group II patients. CRS-R total scores are plotted for the patients who were studied longitudinally (Group II) and eventually emerged from a minimally conscious state (EMCS, **A**) or remained in a vegetative state (VS, **B**); the first assessment (Session 1) was carried out 48 h after withdrawal of sedation, as patients exited from coma. The symbols indicate the associated clinical diagnosis (filled circles = vegetative state; filled triangles = minimally conscious state; filled

(continued)

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Following Session 1, two additional TMS/EEG sessions were performed in the three patients who eventually recovered consciousness: Session 2 was recorded as soon as they satisfied the CRS-R criteria for minimally conscious state and Session 3 when they recovered functional communication and emerged from the minimally conscious state. In these patients, TMS triggered a complex pattern of activation that sequentially involved a large set of cortical areas already during Session 2; this response was substantially different from the simple, local activation of Session 1 and was instead comparable to the one obtained in Session 3, when subjects had recovered their ability to communicate (Figs 2A and 3 and Supplementary Fig. 3A). In the two patients who did not show any clinical improvement beyond vegetative state, a second TMS/EEG measurement (Session 2) was performed >1 month after Session 1 and showed either a local, simple wave of activation (Patient 16) or no response (Patient 17, anoxic), although subjects were awake and open-eyed when their brains were stimulated (Figs 2B, 3, Supplementary Fig. 3B and 4). The results of Group II experiments are also reported in Fig. 3 and indicate that the breakdown of effective connectivity observed in patients in a vegetative state can be reversible and that a substantial improvement in the brain's ability to sustain internal communication occurs at an early stage during recovery of consciousness, before reliable communication can be established with the patient.

The recovery of cortical effective connectivity is not contingent on overt changes in the background electroencephalogram spectrum

Patients in a vegetative state showed a local response to TMS whether they were behaviourally 'awake' (eyes open) or 'asleep' (eyes closed) (Supplementary Fig. 5), suggesting a dissociation between the mechanisms of cortical integration and behavioural arousal. Therefore, we assessed whether changes in effective connectivity could also be dissociated from changes in electrophysiological arousal (EEG activation). Spectral analysis of spontaneous EEG (see 'Materials and methods' section) showed, at the group-level, a significant increase of high-frequency oscillations (α- and β-bands) in locked-in syndrome-emergence from minimally conscious state compared with the minimally conscious state (one-way ANOVA testing group differences, followed by *post hoc* Bonferroni corrected *t*-test) (Supplementary Table 3). In contrast, in spite of a clear-cut change in the electrical response to TMS, no systematic changes of the background EEG could be detected between vegetative state and minimally conscious state both at single subject (Fig. 4) and at the group level (Supplementary Table 3), consistent with previous reports (Kotchoubey *et al.*, 2005). These results suggest that the transition from vegetative to minimally conscious state involves a substantial improvement of effective connectivity that is not necessarily associated with an obvious change in the level of activation of the ongoing EEG.

Discussion

In this work we employed TMS/EEG to measure cortical effective connectivity at the bedside of patients emerging from coma after severe brain injury. The specific aim of the present study was to develop a novel approach to detect and track the neural correlates of recovery of consciousness in non-communicating patients. This approach can complement event-related EEG potential protocols and functional MRI active paradigms because it does not rely on a subject's ability to process sensory stimuli, to understand and follow instructions or communicate; instead, it aims at gauging directly the ability of distributed thalamocortical modules to interact among each other on a millisecond time-scale, a condition that is considered critical for consciousness to emerge (Tononi, 2004; Laureys, 2005; Tononi and Koch, 2008; Alkire *et al.*, 2008; Seth *et al.*, 2008). Practically, such an approach can be important because the capacity of brain-injured patients to interact with the external environment may be impeded by lesions of sensory/motor pathways and cortices, by difficulties in language comprehension (Majerus *et al.*, 2009) and may fluctuate significantly over time (Monti *et al.*, 2010*b*). It could prove especially useful in patients at the lower boundary of consciousness, by providing an objective biomarker that could be used to monitor and guide their rehabilitation and treatment (Schiff, 2010; Shah and Schiff, 2010).

As in previous studies (Massimini *et al.*, 2005, 2010; Ferrarelli *et al.*, 2010), in order to probe the ability of distributed thalamocortical modules to interact, we stimulated a subset of cortical neurons with TMS and performed EEG source modelling to detect, on a millisecond time-scale, the chain of effects triggered

Figure 2 Continued
squares = emergence from minimally conscious state). Coloured arrow tips mark the days when TMS/EEG recordings were performed and the time of TMS delivery (black = Session 1; blue = Session 2; red = Session 3). For every patient and measurement, averaged potentials triggered by TMS (vertical dashed lines) of parietal cortex and recorded from the electrode under the stimulator are shown. The corresponding spread and the time-course of the cortical currents evoked by TMS is measured. The sources involved by maximum neuronal currents during the significant post-stimulus period are plotted on the cortical surface and colour-coded according to their location in six anatomical macro-areas (Fig. 1); the number of detected sources is indicated at the *top right* of each map. The time-series represent TMS-evoked cortical currents recorded from an array of six sources (see their locations in Fig. 1) located ~2 cm lateral to the midline, one for each macro-area. The white crosses mark the sites of stimulation; in each patient, the left parietal cortex was stimulated when patients entered a vegetative state from coma (Session 1), soon after transition to a minimally conscious state or at least 30 days of permanence in a vegetative state (Session 2) and after emergence from a minimally conscious state (Session 3), when subjects recovered functional communication. See Supplementary Fig. 3 for the remaining cortical sites targeted in patients from Group II. EEG positivity is upward.

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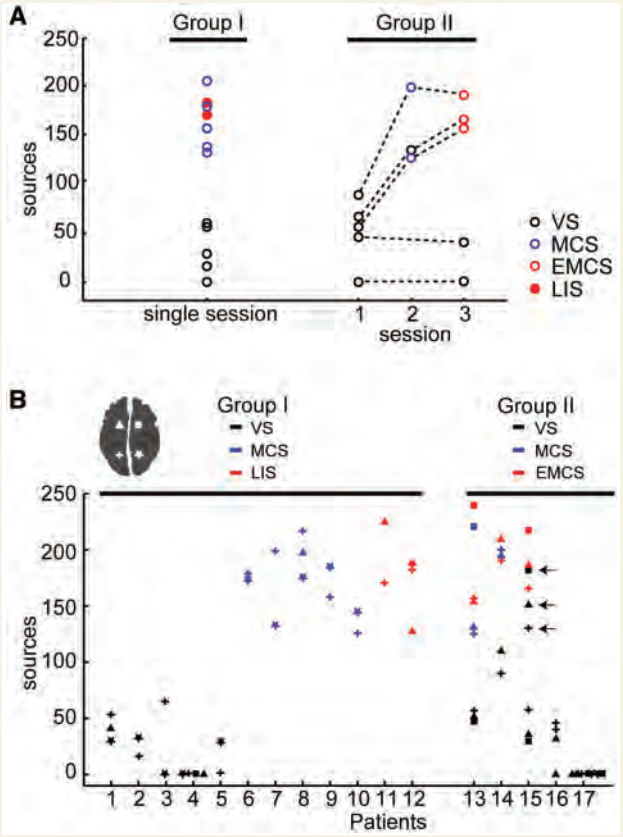


Figure 3 Effective connectivity for all patients and TMS/EEG measurements. (**A**) For each patient and TMS/EEG measurement (same measurements as Figs 1 and 2), the number of sources involved by TMS-evoked currents are plotted. The circles indicate the clinical diagnosis at the time of recording [open black circles for vegetative state (VS); open blue circles for minimally conscious state (MCS); open red circles for emergence from minimally conscious state (EMCS) and filled red circles for locked-in syndrome (LIS)]. (**B**) The number of cortical sources involved by maximum cortical currents detected in all TMS/EEG measurements ($n = 72$) is plotted for all patients (Group I on the *left* and Group II on the *right*). Each value refers to one cortical target and is marked according to both the site of stimulation (the correspondence between symbols and stimulation sites is graphically reported on the cortical map in the *left* upper corner) and the CRS-R diagnosis at the time of recording (black for vegetative state; blue for minimally conscious state; red for locked-in syndrome in Group I and emergence from minimally conscious state in Group II). In all cases, effective connectivity is higher in patients who showed some level of consciousness (minimally conscious state, emergence from minimally conscious state and locked-in syndrome) compared to patients in a vegetative state. An exception is represented by the three measurements (left parietal, left frontal, right frontal) performed in Patient 15 during Session 2 (open black circles indicated by arrows). This patient was diagnosed as being in a minimally conscious state the day before the measurement, slipped back into a behavioural vegetative state on the day of Session 2 and within days, was reassessed clinically as being in a minimally conscious state and then emerged from minimally conscious state (during Session 3). Effective connectivity was null in the two anoxic subjects (Patient 4 from Group I and Patient 17 from Group II).

in the rest of the brain by this initial perturbation. Compared to methods based on the observation of resting brain activity, this perturb-and-measure approach (Paus, 2005) readily dissociates functional connectivity (temporal correlations) from effective connectivity (causal interactions), which is defined as the ability of a subset of neurons to causally affect the activity of other groups of neurons (Friston, 2002; Lee *et al.*, 2003). Recent studies have shown that by employing TMS/EEG and source modelling it is possible to detect patterns of effective connectivity that are generally predicted by main anatomical pathways (Ilmoniemi *et al.*, 1997; Litvak *et al.*, 2007; Morishima *et al.*, 2009; Casali *et al.*, 2010). On the other hand, since TMS tends to activate a large set of cortical axons in a way that is difficult to control fully (Wagner *et al.*, 2007), this technique is more likely to provide a coarse rather than a fine-grained estimation of effective connectivity. In the present context, a broader estimation of effective connectivity may constitute an advantage, since theoretical works (Tononi, 2004; Tononi and Koch, 2008), experimental data (Maandag *et al.*, 2007; Alkire *et al.*, 2008; Shulman *et al.*, 2009) and clinical evidence (Markowitsch and Kessler, 2000; Mataro *et al.*, 2001; Schiff, 2010) suggest that consciousness depends not so much on some specific circuits, but rather on the capacity of distributed regions of the brain to interact through divergent cortico–cortical and cortico–thalamo–cortical connections. Indeed, as demonstrated by previous experiments, TMS/EEG measures of effective connectivity can distinguish readily between conditions in which consciousness is present (alert wakefulness, dreaming) (Massimini *et al.*, 2005, 2010) and conditions in which consciousness is reduced, or lost (sleep and anaesthesia) (Massimini *et al.*, 2005; Ferrarelli *et al.*, 2010).

Figure 3 summarizes the results obtained after applying TMS in all 17 patients and shows that it is possible to discriminate reliably between a vegetative and minimally conscious state, at the single-subject level. Crucially, this discrimination was achieved in a way that is completely independent on the patient's ability to exchange information with the surrounding environment. The fact that TMS/EEG detected a clear-cut difference between vegetative state and minimally conscious state (unconsciousness versus low-level of consciousness) but not between minimally conscious state, emergence from minimally conscious state and locked-in syndrome (lower versus higher levels of consciousness) suggests that the availability of effective interactions among thalamocortical modules may be a critical mechanism that correlates closely with the presence/absence of a minimal level of consciousness. This aspect is particularly relevant if one considers that the most challenging task at the bedside is distinguishing between patients in a vegetative state and non-communicating patients in a minimally conscious state (Majerus *et al.*, 2005). As an example, in the present work, TMS/EEG detected the resumption of rapid, effective intracortical interactions in the brain of a patient (Patient 15) who (during Session 2) had temporarily slipped back into a clinically vegetative state, possibly due to transient fluctuations in her ability to interact with the environment; this patient was reassessed clinically as minimally conscious state and then emerged from minimally conscious state.

Clearly, validating an objective marker of consciousness that can be applied to patients that are unable to interact with the external

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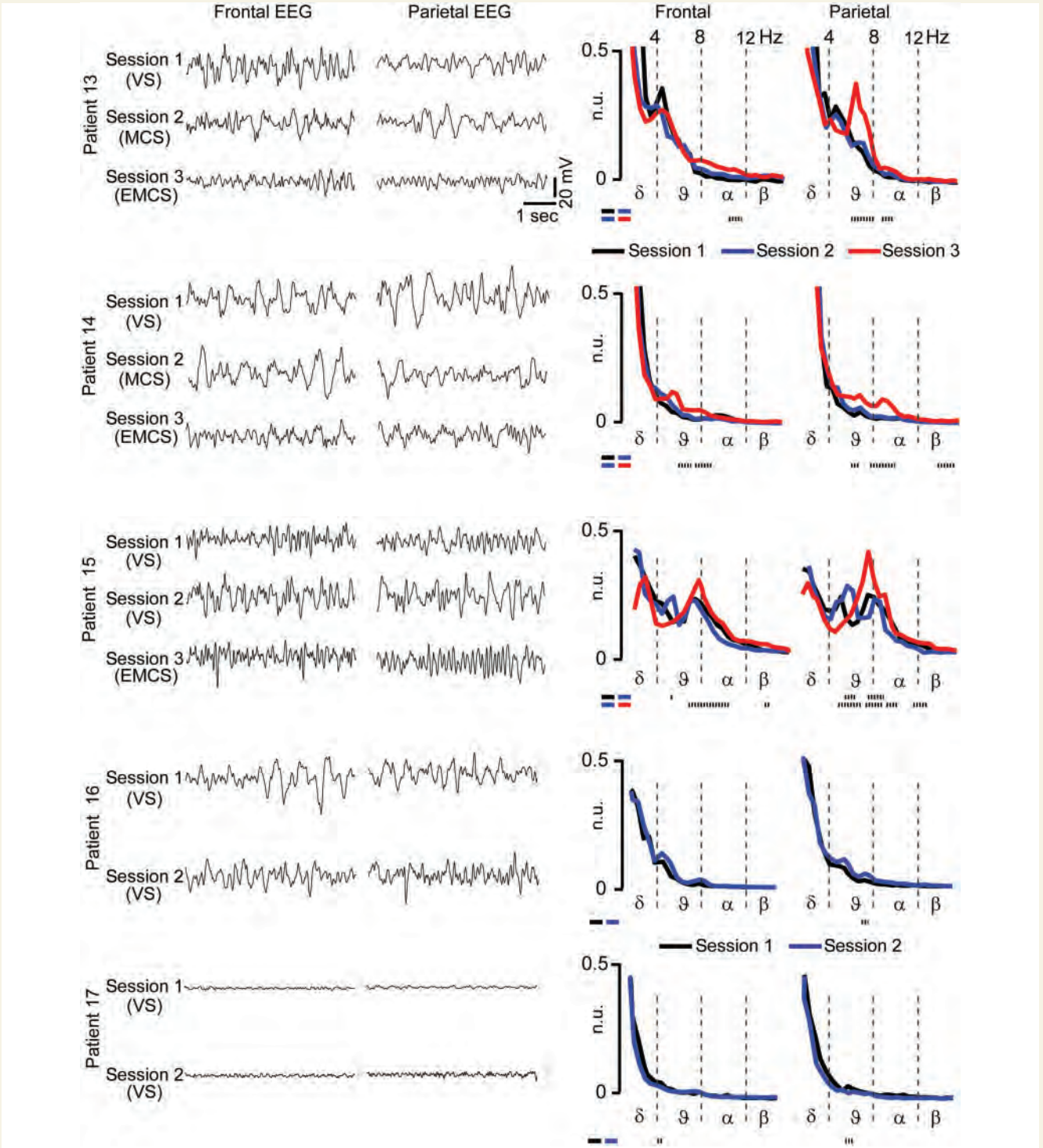


Figure 4 EEG spectra show evident changes from minimally conscious state (MCS) to emergence from minimally conscious state (EMCS) but not from vegetative state (VS) to minimally conscious state. Spontaneous EEG traces (5 s) and EEG spectra (calculated on 2 min; average of 5 s epochs) are shown for the five subjects who underwent longitudinal recording sessions (Group II); in these patients, changes in the EEG spectrum were assessed statistically by means of a two-tailed paired *t*-test. The dotted lines at the bottom of each plot indicate the frequency bins that show statistically significant differences of power (*t*-test, $P < 0.01$). EEG positivity is upward. n.u. = normalised units.

environment is challenging by definition, since, in these cases, there is no behavioural reference to assess the presence of consciousness. In an attempt to overcome this circularity, we have previously tested TMS/EEG measures in states in which consciousness is unambiguously present [alert wakefulness (Massimini *et al.*, 2005), dreaming (Massimini *et al.*, 2010)] or unambiguously reduced [early slow wave sleep (Massimini *et al.*, 2005), general anaesthesia (Ferrarelli *et al.*, 2010)]. Here, we

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demonstrate that TMS/EEG measures are reliable when they are applied to brain-injured patients with a stable clinical diagnosis (Group I) and that they are sensitive in detecting a clear-cut resurgence of cortical effective connectivity in the brains of individual patients who gradually recover consciousness and functional communication (Group II). In future works, the same approach should be further tested, in a back-and-forth process, both in definite and in ambiguous clinical conditions, such as the one of Patient 15. It will be equally important to directly compare the ability of TMS/EEG to discriminate between vegetative and minimally conscious states at the individual level with the diagnostic capacity of other neurophysiological methods, such as peripherally evoked potentials (Kotchoubey *et al.*, 2005; Bekinschtein *et al.*, 2009; Fischer *et al.*, 2010; Boly *et al.*, 2011) and long-term EEG recordings (Landsness *et al.*, 2011). The lack of a direct comparison with other techniques represents a clear limitation of the present study and is due to logistical and time constraints (in each patient, we stimulated from two to four cortical sites) in the intensive care unit. For now, we can only compare the present results to the current literature and, in particular, to a number of works in which the mismatch negativity was evaluated systematically in patients in a vegetative state and patients in a minimally conscious state. Altogether, this body of literature suggests that, while the mismatch negativity may differ significantly between vegetative state and minimally conscious state at the group level, it does not discriminate reliably between these two conditions at the individual patient's level; in fact, this late component may be undetectable in a large proportion (up to 60%) of patients who are behaviourally in a minimally conscious state (Kotchoubey *et al.*, 2005; Fischer *et al.*, 2010; Holler *et al.*, 2011). Since in the present study we found consistent TMS/EEG results across sites of stimulation, in future work it will be feasible to directly compare the EEG response to TMS of a single cortical area with a battery of sensory evoked potentials (N20, mismatch negativity and P3b) recorded in the same patient, on the same day. These joint measurements will be crucial to precisely quantify the relative diagnostic power of complementary neurophysiological techniques that may enter the routine evaluation of severely brain-injured patients. To this regard, the present experiments show that, like peripheral evoked potentials, TMS-evoked potentials can be recorded at the patient's bedside, in the intensive care unit. A technical disadvantage of TMS/EEG is that it requires a more complex set-up, which includes a TMS main unit, a TMS-compatible EEG amplifier and, ideally, a navigation system in order to precisely target TMS on the cerebral cortex. Navigating TMS based on prior anatomical knowledge (CT or MRI scan) may be especially important in the assessment of brain-injured patients for two reasons. First, because it allows avoiding obvious cortical lesions and stimulating the cortical surface at supra-threshold intensity (see 'Materials and methods' section and Casali *et al.*, 2010) and second (and most important) because it ensures high test-retest reproducibility when TMS-evoked potentials are performed longitudinally (Lioumis *et al.*, 2009; Casarotto *et al.*, 2010). Hardware solutions aside, developing TMS/EEG towards routine clinical applications may require the implementation of a standard, fast data analysis procedure to calculate the spatial-temporal complexity of the cortical response to TMS.

Besides their potential diagnostic value, TMS/EEG measurements may provide novel insights on the physiopathology of disorders of consciousness as well as a valuable marker to guide rehabilitation and treatment (Giacino *et al.*, 2006; Shah and Schiff, 2010). In patients in a vegetative state, who were aroused but unaware, TMS failed to trigger complex, long-range activations pointing to a dissociation between arousal and the mechanisms of thalamocortical integration. In patients in a vegetative state caused by anoxia (Patients 4 and 17) no significant EEG responses could be elicited, even when TMS was delivered at high intensity at multiple stimulation sites (Fig. 3 and Supplementary Fig. 4), consistent with an extensive necrosis of the cerebral cortex (Kinney and Samuels, 1994). In non-anoxic patients in a vegetative state TMS elicited, at both frontal and parietal sites, a strong response that remained local (Figs 1, 2, Supplementary Fig. 2 and 3) corroborating the notion that the brain of these patients may retain islands of cortex (including associative areas) that are responsive, but reciprocally disconnected (Schiff *et al.*, 2002; Laureys *et al.*, 2004). According to post-mortem (Adams *et al.*, 2000) and *in vivo* (Fernandez-Espejo *et al.*, 2011) neuropathological studies, this disconnection is primarily structural and may be largely due to widespread injury of cortico–cortical fibres but also to thalamic damage, leading to a substantial impairment of cortico–thalamo–cortical circuits. Notably, the present results indicate that, in addition to the anatomical damage, functional disturbances in thalamocortical networks may play a significant role. Indeed, in non-anoxic patients in a vegetative state TMS triggered a slow wave similar to the one recorded during sleep (Massimini *et al.*, 2005, 2007) and anaesthesia (Ferrarelli *et al.*, 2010) suggesting that, besides structural lesions and disconnections, functional alterations such as disfacilitation (Englot *et al.*, 2010), network bistability (Massimini *et al.*, 2009*b*) and altered excitation–inhibition balance (Schiff, 2010), may contribute to the overall impairment of effective connectivity. These alterations were possibly reversed in the patients of Group II in whom repeated TMS/EEG measurements revealed a resumption of fast, long-range interactions, which paralleled recovery of consciousness; further measurements should be performed, longitudinally, at the bedside of patients who recuperate spontaneously and in patients who undergo pharmacological treatment (Brefel-Courbon *et al.*, 2007), or protocols of neuromodulation (Schiff *et al.*, 2007), in order to gain better insight on the mechanisms of recovery of consciousness after brain injury.

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Supplementary material

Supplementary material is available at *Brain* online.

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Supplementary Material for:

Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients

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Supplementary Table 1: *Group I patients*

	Clinical features				CRS-R								
	Sex (age, years)	**Cause**	**Outcome at 6 months**	**Time of TMS/EEG (days after insult)**	**Diagnosis at time of TMS/EEG**	**Auditory function**	**Visual function**	**Motor function**	**Oromotor/Verbal function**	**Communication**	**Arousal**	**Total score**	**CT/MRI**
Patient 1	Male (81)	CVA	GOS 1	19	VS	None	None	Flexion to pain	Oral reflexes	None	Without stimulation	5	Multiple ischemic lesions of right sylvian areas, left posterior hemisphere, corpus callosum, left thalamus, brainstem and cerebellum. Right sylvian atrophy.
Patient 2	Male (68)	Trauma	GOS 1	21	VS	None	None	Flexion to pain	None	None	Without stimulation	4	Hemorrhagic contusion of bilateral frontal lobes and left peri-cerebellar lesions.
Patient 3	Female (83)	Trauma	GOS 1	14	VS	Startle reflex	None	Abnormal posturing	None	None	With stimulation	3	Bilateral frontal subarachnoidal hemorrhage, right temporo-fronto-parietal and left parietal subdural hematoma.
Patient 4	Female (15)	CRA	GOS 1	23	VS	Startle reflex	None	Abnormal posturing	Oral reflexes	None	Without stimulation	5	Diffuse bilateral lesions in lenticular, caudate, thalamic and fronto-parietal white matter.
Patient 5	Male (19)	Trauma	GOS 2	172	VS	Startle reflex	None	Abnormal posturing	Oral reflexes	None	Without stimulation	5	Left subdural hemorrhage. Large lesion of the pons, left cortical and subcortical structures and corpus callosum. Periventricular leucoencephalopathy and ex-vaquo hydrocephalus.
Patient 6	Female (76)	Subarachnoid hemorrhage	GOS 3	28	MCS	Startle reflex	Visual pursuit	Flexion to pain	Vocalization/ Oral movement	None	Without stimulation	10	Subarachnoid hemorrhage of posterior fossa extending to left diencephalon associated with hydrocephalus.
Patient 7	Male (72)	CVA	GOS 3	38	MCS	Reproducible movement to command	Object recognition	Flexion to pain	Vocalization/ Oral movement	Non-functional: Intentional	With stimulation	14	Left cerebellar ischaemic-hemorragic lesions extending to mesencapjhalon.

Patient 8	Male (20)	Trauma	GOS 3	1334	MCS	Reproducible movement to command	Visual pursuit	Abnormal posturing	Oral reflexes	None	Without stimulation	10	Right lenticular and caudate nuclei lesions. Bilateral periventricular leucoencephalopathy and atrophy of frontal and temporal lobes, bilateral thalami and mesopontine region. Ex-vaquo quadriventricular hydrocephalus.
Patient 9	Female (38)	Trauma	GOS 3	12	MCS	Reproducible movement to command	Visual pursuit	Automatic motor response	Vocalization/ Oral movement	Non-functional: Intentional	With stimulation	15	Right subdural hematoma. Bilateral inferior frontal and right temporo-parieto-occipital lesions.
Patient 10	Male (62)	Subarachnoid hemorrhage	GOS 4	20	MCS	Startle reflex	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation	9	Anterior interhemispheric and bilateral sylvian subarachnoid hemorrhage, predominantly on the right side extending to the basal cistern.
Patient 11	Male (45)	CVA	GOS 3	35	LIS	Systematic movement to command	Object recognition	None	Oral reflexes	Functional: Accurate	Attention	15	Ischemic lesions in left cerebellar hemispheric and left cerebral peduncle regions.
Patient 12	Female (25)	CVA	GOS 3	1399	LIS	Systematic movement to command	Object recognition	Flexion to pain	Vocalization/ Oral movement	Functional: Accurate	Attention	18	Bilateral centro-pontine , thalamic, cerebellar and occipito-cerebellar, ischemic lesions.

GOS=Glasgow Outcome Scale; VS=vegetative state, MCS=minimally conscious state, LIS=locked-in syndrome; EMCS=emergence of the minimally conscious state; CRS-R=Coma Recovery Scale-Revised, CT/MRI:computed tomography/magnetic resonance imaging; CRA cardio respiratory arrest, CVA cerebrovascular accident

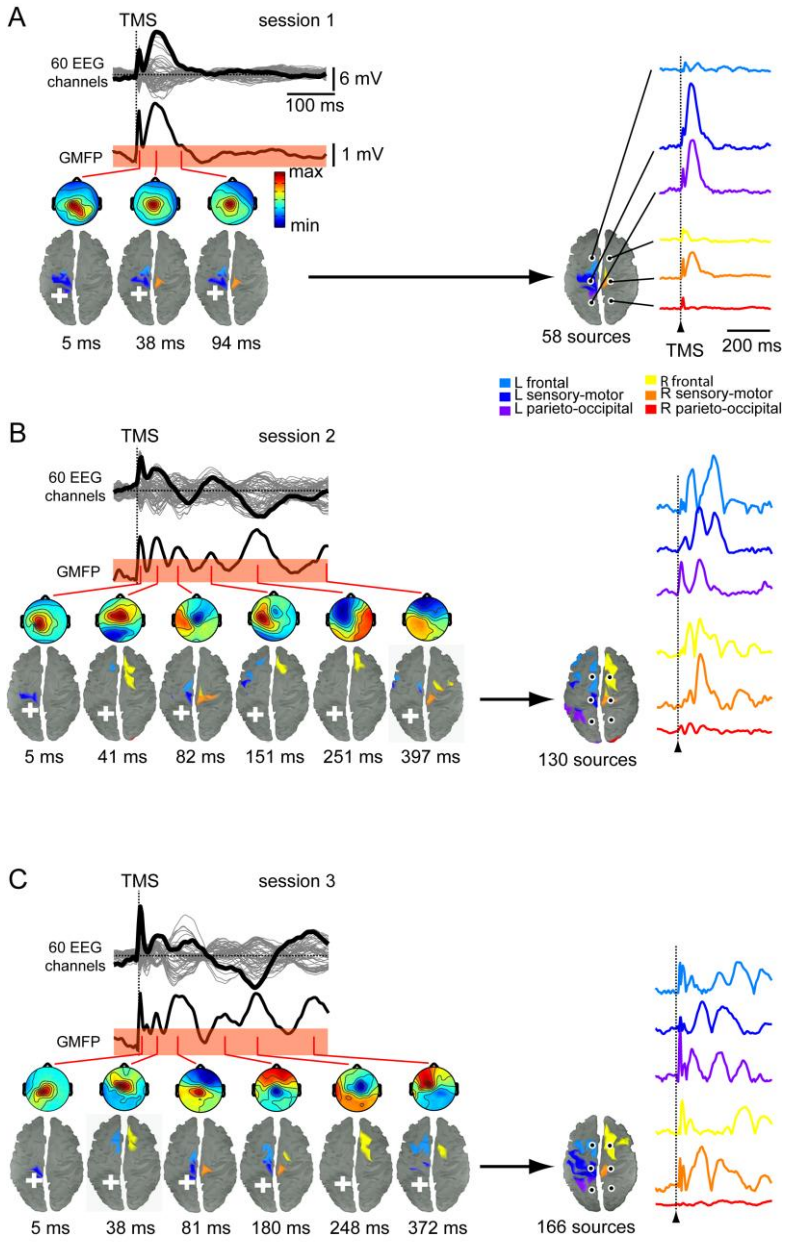
Note that CRS-R are relative to the day when TMS/EEG session was performed

Supplementary Table 2: *Group II patients*

		Clinical features				CRS-R								
	TMS/EEG session	Sex (age, years)	Cause	Outcome at 6 months	Time of TMS/EEG (days after insult)	Diagnosis at time of TMS/EEG	Auditory function	Visual function	Motor function	Oromotor/Verbal function	Communication	Arousal	Total score	CT/MRI
Patient 13	1	Female (60)	CVA	GOS 3	15	VS	None	None	Flexion to pain	Vocalization/ Oral movement	None	With stimulation	5	Right fronto-temporo-parietal intracerebral hemorrhage with mass effect.
	2				23	MCS	Reproducible movement to command	None	Flexion to pain	Oral reflexes	Non-Functional: Intentional	With stimulation	8	
	3				30	EMCS	Systematic movement to command	Object recognition	Functional use of objects	Vocalization/ Oral movement	Functional: Accurate	With stimulation	20	
Patient 14	1	Male (16)	Trauma	GOS 3	12	VS	None	None	Flexion to pain	None	None	With stimulation	3	Brainstem lesion (right cerebellar peduncle). Left occipito-temporal hemorrhagic contusions and right occipital lesions.
	2				19	MCS	Reproducible movement to command	None	Automatic motor reaction	Vocalization/ Oral movement	None	Without stimulation	12	
	3				40	EMCS	Systematic movement to command	Object recognition	Automatic motor reaction	Vocalization/ Oral movement	Functional: Accurate	Attention	21	
Patient 15	1	Female (60)	CVA	GOS 3	35	VS	None	None	Abnormal posturing	Oral reflexes	None	With stimulation	3	Right ponto-mesencephalic ischemic lesion and bilateral frontal and peri-cerebellar subdural collections. Subarachnoid hemorrhage in lateral ventricles.
	2				46	VS*	None	Blink to threat	Flexion to pain	Oral reflexes	None	With stimulation	5	
	3				56	EMCS	Reproducible movement to command	Visual pursuit	Object manipulation	Intelligible verbalization	Functional: Accurate	With stimulation	16	
Patient 16	1	Female (77)	Subarachnoid hemorrhage	GOS 2	25	VS	Startle reflex	None	Abnormal posturing	Oral reflexes	None	With stimulation	4	Ruptured aneurysm of left anterior communicating artery with subarachnoid hemorrhage, diffuse periventricular ischemic lesions and hydrocephalus.
	2				44	VS	Startle reflex	None	Flexion to pain	Oral reflexes	None	With stimulation	5	
Patient 17	1	Male (43)	CRA	GOS 2	22	VS	None	None	Flexion to pain	Oral reflexes	None	Without stimulation	5	Ischemic -lesions in basal ganglia and insula.
	2				62	VS	Startle reflex	None	Abnormal posturing	Oral reflexes	None	Without stimulation	5	

* Note that the day before, Patient 15 was diagnosed MCS with reproducible movement to command and visual pursuit (total score of 9); CRA cardio respiratory arrest, CVA cerebrovascular accident

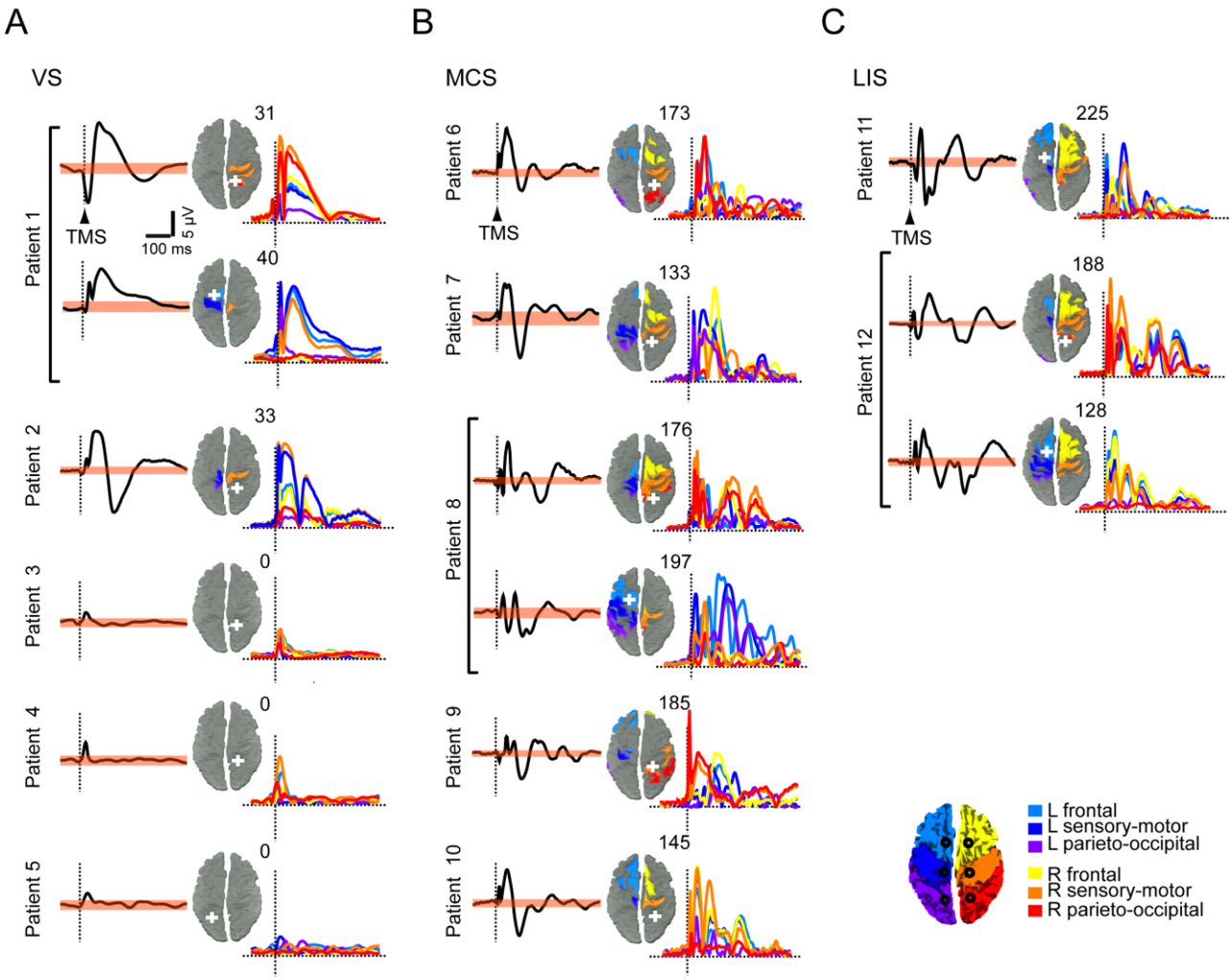
Supplementary Figure 1: *Detection of TMS-evoked maximum cortical currents*



In this example, scalp voltages and currents induced by TMS of left parietal cortex (white crosses) in Patient 15 during session 1 (panel A), session 2 (panel B), and session 3 (panel C) are shown. In each panel, the top traces represent averaged TMS-evoked potentials recorded at all electrodes, superimposed in a butterfly plot (grey traces; the black trace highlights the response recorded at the electrode under the stimulator). Below, the global mean field power (GMFP) is depicted; the upper boundary of the pink area indicates the threshold (bootstrap; $p<0.01$) above which the global response to TMS is considered significant. The maps underneath show the topographies of scalp voltage calculated at the peaks of the significant GMFP. At the bottom, the corresponding cortical maps of maximal neuronal currents are depicted. At each time point, the 10 most active cortical sources are plotted and colored according to their anatomical position (Cyan=Left frontal; dark blue=Left sensory-motor; purple=Left parieto-occipital; yellow=Right frontal; orange=Right sensory-motor; red=Right parieto-occipital. See color legend). Counting and plotting the sources involved by maximum neuronal currents across all significant time points resulted in the cortical maps and in the values reported in Fig. 1, Fig. 2, Fig. 3 and Supplementary Figs. 2, 3, 5. Vertical dashed lines mark the time of stimulation. EEG positivity is upward.

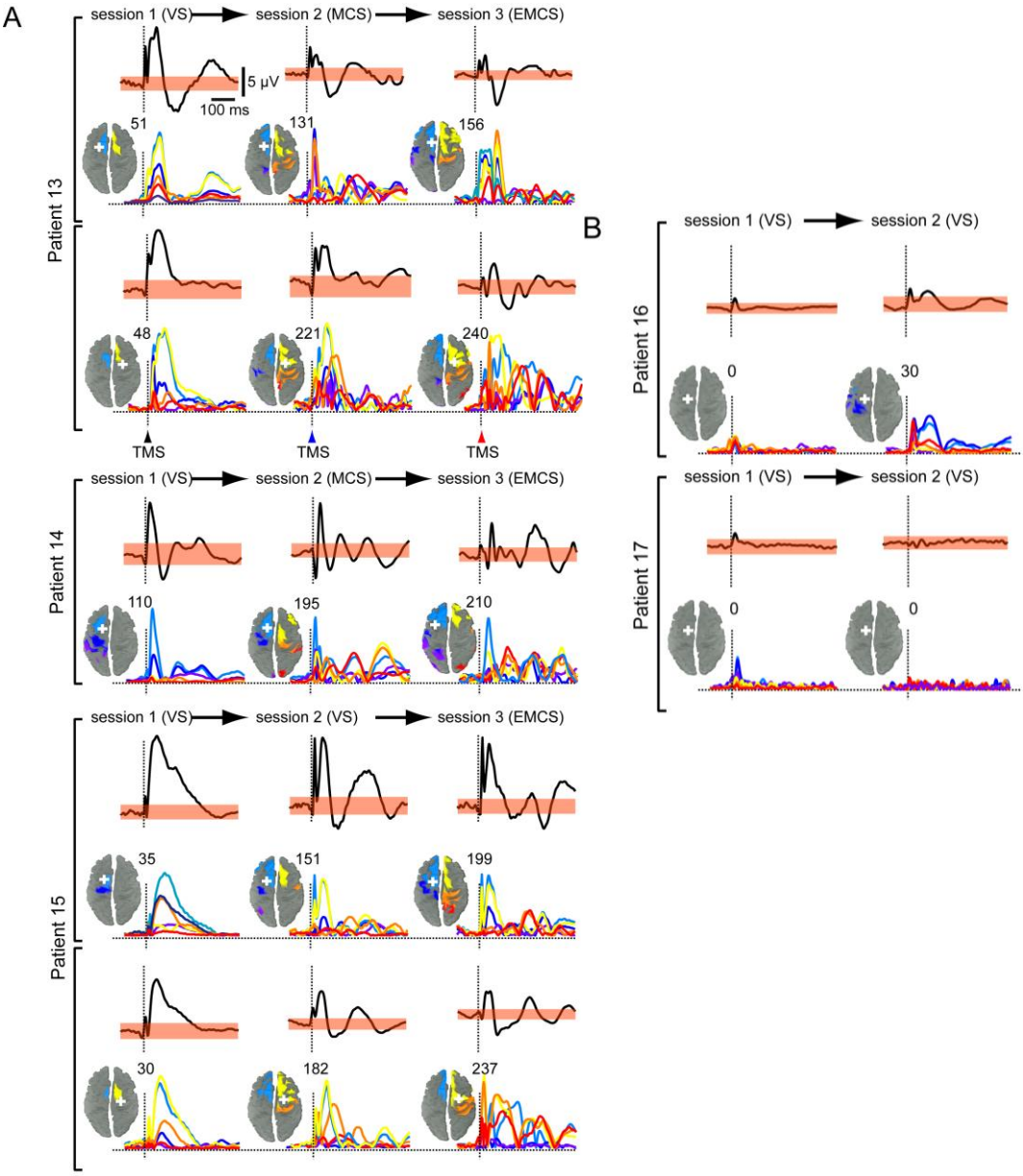
SUPPLEMENTARY RESULTS

Supplementary Figure 2: *Additional TMS/EEG measurements in Group I patients.*



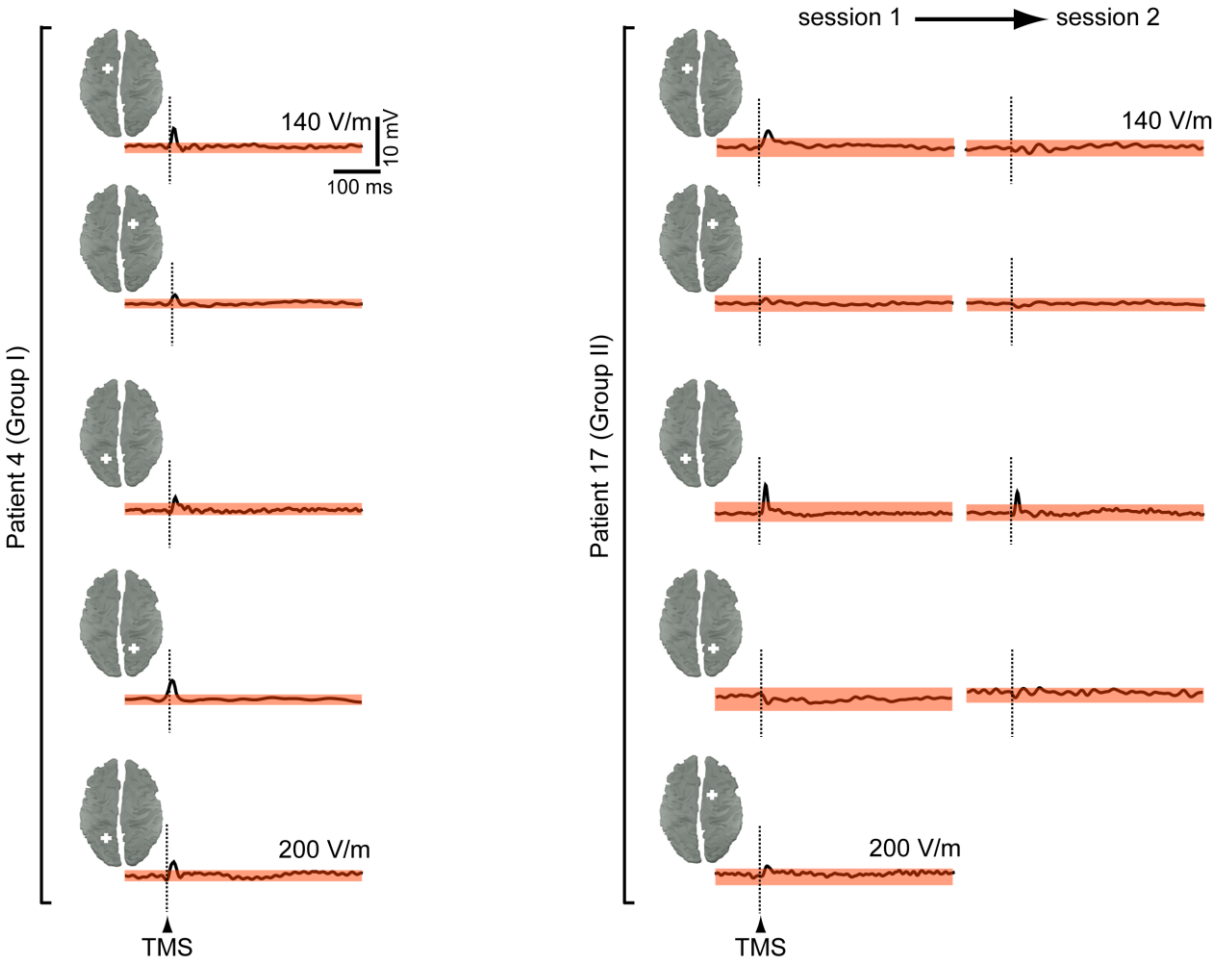
EEG responses to right parietal and left frontal stimulations are reported. For each patient and stimulation, the averaged TMS-evoked potentials recorded at one electrode under the stimulator (black trace) and the respective significance threshold (upper and lower boundaries of the pink bands; bootstrap statistics, $p<0.01$) are shown. As in Fig.1 the sources engaged by maximum cortical currents (10 most active sources) during the significant post-stimulus period of the GMFP are plotted on the cortical surface and color-coded according to their location in six anatomical macro-areas as indicated in the legend; for each map the total number of detected sources is displayed. The time-series represent TMS-evoked cortical currents recorded from an array of 6 sources (black circles on the bottom-right cortical map) located about 2 cm lateral to the midline, one for each macro-area. EEG positivity is upward. As was the case for the measurements reported in Fig.1, TMS triggered a simple and local response, or no response at all, in VS patients and a complex, widespread response in MCS and LIS patients.

Supplementary Figure 3: *Additional TMS/EEG measurements in Group II patients.*



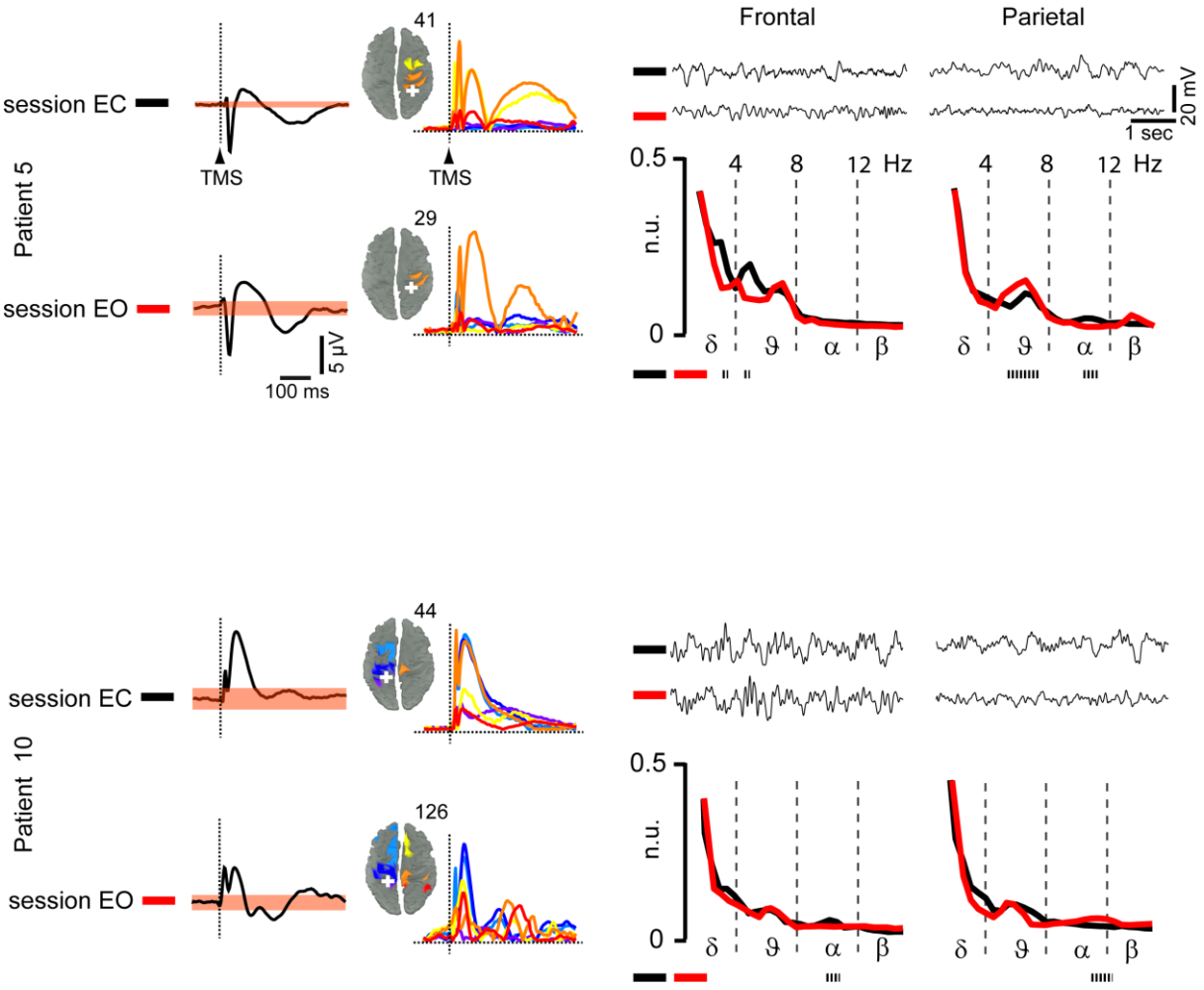
EEG responses obtained after stimulation of the left and right frontal cortex are reported. As in Fig. 2, for every patient and session, averaged potentials triggered by TMS (vertical dashed lines) at the electrode under the stimulator are shown (significance threshold is indicated by the pink area). The sources involved by maximum neuronal currents during the significant post-stimulus period are plotted on the cortical surface and color-coded according to their location in six anatomical macro-areas (see Supplementary Fig. 2); the number of detected sources is indicated at the top-right end of each map. The time-series represent TMS-evoked cortical currents recorded from an array of 6 sources (see their locations in Fig.1 and Supplementary Figs 1 and 2) located about 2 cm lateral to the midline, one for each macro-area. EEG positivity is upward. Similarly to Fig. 2, this figure shows that when a patient recovers consciousness (EMCS), a clear-cut change in effective connectivity occurs already during the transition from VS to MCS. On the contrary, this change does not occur in patients that stay VS (Patients 16 and 17) and are recorded one month apart the first session.

Supplementary Figure 4: *In anoxic, VS patients TMS fails to trigger significant responses*



According to the general experimental procedure, each patient was stimulated, at different sites and at different intensities, until a significant EEG response could be elicited. In most VS patients TMS triggered a significant response in at least one cortical area; this response was invariably characterized by a simple TMS-evoked wave of activation and by maximum cortical currents that were confined to the stimulated cortical area. However, in two out of 10 VS patients (Patient 4 and Patient 17), TMS failed to elicit any significant response even when several stimulations were carried out at multiple cortical sites and at increasing intensities. As in previous figures, black traces indicate the EEG channel under the stimulator, while pink areas indicate the significance level (bootstrap, $p<0.01$). In all cases, TMS failed to elicit a significant activation, even when TMS was delivered at an intensity of 200 V/m on the cortical surface, an electric field four times larger than the one normally required to elicit a significant EEG response. Interestingly, Patient 4 and Patient 17 entered the VS as a consequence of a general anoxia caused by a cardiac-respiratory arrest (CRA, Supplementary Tables 1 and 2). Thus, TMS in VS patients either triggers a simple and local response, or no response at all. While the first occurrence seems to indicate that cortical circuits are reactive but somehow dysfunctional, the second one may signal a widespread loss of cortical neurons in an anoxic, apallic patient.

Supplementary Figure 5: *Arousal is dissociated from cortical integration in VS patients.*



In the present study, TMS/EEG and background EEG recordings were always carried out while patients were behaviorally awake (eyes open, EO). If subjects showed signs of sleepiness (prolonged eye closure, EC), the CRS-R arousal facilitation protocol was applied, or the experiment was suspended. However, in two cases, one VS (Patient 5) and one MCS (Patient 10), we recorded TMS-evoked potentials and spontaneous EEG both during behavioral sleep and wakefulness. During behavioral sleep (EC) both patients showed a simple, local wave of activation similar to the one typically observed in sleeping or anesthetized healthy subjects. However, while both patients showed some signs of EEG activation (a slight shift towards faster frequencies of the spectral peaks) during the transition from sleep to wakefulness, only the MCS patients recovered a widespread and complex EEG response to TMS. These results suggest that in VS patients the mechanisms of behavioral and EEG arousal can be dissociated from the ones of cortical integration and that brainstem activating systems are not sufficient to re-establish a minimal level of consciousness, unless effective connections among cortical modules are available.

Supplementary Table 3: *Spontaneous EEG activity do not discriminate between VS and MCS, at the group level*

	VS (1)	**MCS** (2)	**EMCS-LIS** (3)	ANOVA			*p* Value for Comparison		
Variables	Mean (± std)	Mean (±std)	Mean (±std)	*df*	*F*	*p*	1 vs. 2	2 vs. 3	1 vs. 3
Frontal Delta (n.u.)	0.3025 (±0.1104)	0.2556 (±0.0933)	0.2551 (±0.0711)	2, 20	0.65516	n.s.	n.a.	n.a.	n.a.
Frontal Theta (n.u.)	0.0700 (±0.0523)	0.1148 (±0.0694)	0.1313 (±0.0929)	2, 20	1.6862	n.s.	n.a.	n.a.	n.a.
Frontal Alpha (n.u.)	0.0199 (±0.0279)	0.0298 (±0.0151)	0.0598 (±0.0294)	2, 20	4.4263	0.02	n.s.	n.s.	0.02
Frontal Beta (n.u.)	0.0038 (±0.0035)	0.0079 (±0.0051)	0.0165 (±0.0080)	2, 20	9.6508	<0.01	n.s.	0.02	<0.001
Parietal Delta (n.u.)	0.2257 (±0.1002)	0.2037 (±0.0453)	0.2116 (±0.0900)	2, 20	0.16208	n.s.	n.a.	n.a.	n.a.
Parietal Theta (n.u.)	0.0606 (±0.0529)	0.0807 (±0.0540)	0.1149 (±0.0731)	2, 20	3.6103	n.s.	n.a.	n.a.	n.a.
Parietal Alpha (n.u.)	0.0203 (±0.0348)	0.0290 (±0.0181)	0.0875 (±0.0732)	2, 20	4.6262	0.02	n.s.	n.s.	0.02
Parietal Beta (n.u.)	0.0032 (±0.0023)	0.0062 (±0.0034)	0.0142 (±0.0092)	2, 20	8.8003	<0.01	n.s.	0.02	<0.01

Power spectral densities were calculated for each standard EEG frequency band (Delta, 1-4 Hz, Theta, 4-8 Hz, Alpha, 8-12 Hz and Beta, 12-25 Hz). A one-way ANOVA, followed by post-hoc Bonferroni corrected t-test, was applied separately for each frequency band to detect, at the group level, differences between conditions (VS, MCS and LIS-EMCS). Significance level was set at $p<0.05$. Significant differences were found between MCS and LIS-EMCS conditions in the fast EEG frequency bands (Alpha and Beta ranges). No differences were found between VS and MCS conditions. Abbreviations: n.u., normalized units; n.s., not significant; n.a., not applicable.

gametocytes rescued development of ookinetes to untreated control levels when grown in filtered *Esp_Z* culture medium (Fig. 3B), and parasite development in the presence of replicating *Esp_Z* was rescued by vitC in a dose-dependent fashion (Fig. 3C). Furthermore, reduced glutathione, another potent antioxidant, also rescued in vitro ookinete formation in the presence of *Esp_Z* (fig. S7). We showed that vertebrate leukocytes were not responsible for the observed in vitro ookinete inhibition (fig. S8). More important, supplementing an infectious blood meal with vitC did not affect parasite numbers in the absence of *Esp_Z* but rescued *P. falciparum* ookinete development twofold in the lumen of *A. gambiae* midguts when they were cofed with *Esp_Z* (Fig. 3D). The significant, yet incomplete, rescue of ookinete development with higher bacterial concentrations could be attributed to a variety of factors such as insufficient concentrations of antioxidant to neutralize the higher amount of bacterially produced ROS, excretion of substantial amounts of antioxidant by mosquito diuresis, an intimate association between bacteria and parasites that may not enable detoxification of ROS before parasite inhibition, or the loss of antioxidant activity from prolonged exposure in the digestive environment of the midgut. Antioxidant concentrations higher than 10 mM in the blood meal interfered with mosquito feeding propensity.

Genotypic analyses of laboratory and wild mosquito populations have suggested that a dominant refractory phenotype is associated with innate immunity and that *Plasmodium* infection is a result of immune failure (*21*–*23*). Our studies show a mechanism of *Plasmodium* inhibition that does not involve the mosquito-derived innate immune response, and they support the idea that the native microflora of *Anopheles* mosquitoes plays a crucial role in refractoriness to *Plasmodium* infection and will therefore influence transmission success to humans.

Bacteria of the genus *Enterobacter* have been isolated from many anopheline mosquito species in diverse geographic regions (*3*, *5*, *24*). We show that mosquitoes do not become infected with *Plasmodium* parasites when exposed to an *Enterobacter* bacterium isolated from wild mosquito populations in southern Zambia, and we show that inhibition of parasite development can be mediated by bacterial generation of ROS. Although *Esp_Z* was isolated from a single collection made during one rainy season, 25% of mosquitoes collected harbored the strain. It may be possible to manipulate the composition of the midgut microbial flora in wild mosquitoes to increase the prevalence of *Esp_Z* or other naturally inhibitory bacteria as part of an integrated malaria control strategy.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S8
Tables S1 to S3
References and Notes

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Preserved Feedforward But Impaired Top-Down Processes in the Vegetative State

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Frontoparietal cortex is involved in the explicit processing (awareness) of stimuli. Frontoparietal activation has also been found in studies of subliminal stimulus processing. We hypothesized that an impairment of top-down processes, involved in recurrent neuronal message-passing and the generation of long-latency electrophysiological responses, might provide a more reliable correlate of consciousness in severely brain-damaged patients, than frontoparietal responses. We measured effective connectivity during a mismatch negativity paradigm and found that the only significant difference between patients in a vegetative state and controls was an impairment of backward connectivity from frontal to temporal cortices. This result emphasizes the importance of top-down projections in recurrent processing that involve high-order associative cortices for conscious perception.

The vegetative state (VS) is defined by preserved arousal, in the absence of any behavioral signs of awareness (*1*). In contrast, patients in a minimally conscious state (MCS) show nonreflexive and purposeful behaviors but are unable to communicate (*2*). Because the clinical diagnosis of these patients is extremely difficult (*3*), neuroimaging experiments have tried to establish accurate biomarkers of consciousness level in VS and MCS. These patients also provide a lesion-deficit model in the quest for neural correlates of consciousness in the human brain (*4*). The conscious perception of external stimuli requires activation of frontoparietal cortices, in addition to activity in low-level specialized cortices (*5*–*7*). However, frontoparietal activation can also be found during subliminal stimulus processing (*8*, *9*). Current evidence points to long-latency evoked event-related potential (ERP) components, involving frontoparietal cortices, as a reliable neu-

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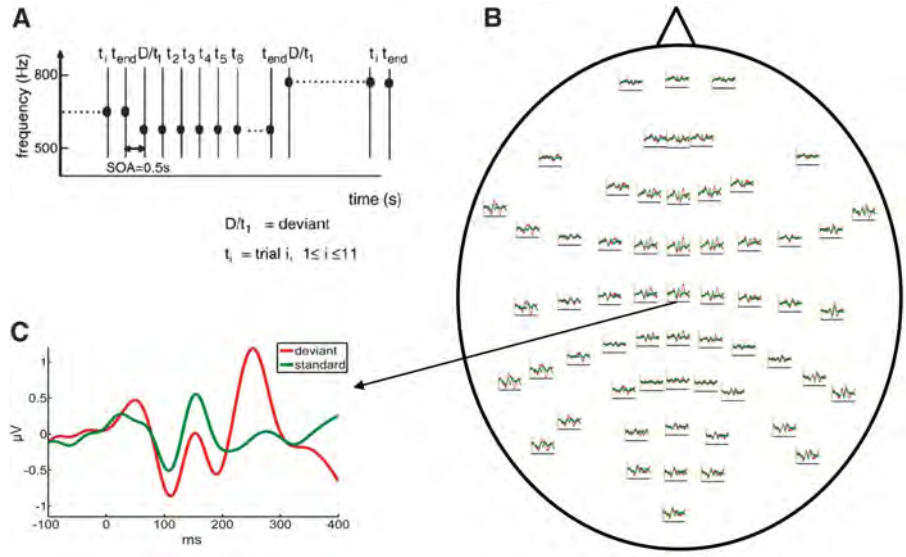


Fig. 1. Design and ERP responses elicited in a roving paradigm. (**A**) The experimental design used a sporadically changing standard stimulus (auditory tone). The first presentation of a novel tone is a deviant D = t_1 that becomes a standard, through repetition; t_2,…,t_{end}. In this paradigm, deviants and standard have exactly the same physical properties. (**B**) Grand-mean (averaged over control subjects) ERP responses to the first and 11th tone presentations: the established "standard" (t_{11} in green) and deviant tone (t_1 in red) overlaid on a scalp map of 60 electroencephalogram electrodes. (**C**) ERP responses to standard and deviant tones at channel Cz (central). Deviant corresponds to responses elicited by the first tone presentation or to oddball events. Standard corresponds to the 11th repetition of the same tone. [Adapted from a figure in M. I. Garrido *et al*. (*22*), with permission from Elsevier]

ronal marker for conscious perception in healthy controls (*10*). Although feed-forward connectivity is sufficient to generate short-latency ERP components, long-latency components are mediated by backward connections (*11*). This suggests that the level of consciousness may rest on the integrity of backward (top-down) connectivity. We used a mismatch negativity (MMN) paradigm, which elicits well-characterized (preattentive) responses (*12*). The MMN correlates inversely with consciousness level during anesthesia (*13*) and with depth of sleep (*14*); although some studies report negative findings (*15*), MMN deficits have also been associated with the level of consciousness in MCS and VS (*16*) [see supporting online material (SOM) text]. We predicted that both long-latency components and backward connectivity would correlate with level of consciousness. We tested this hypothesis quantitatively, using Dynamic Causal Modeling (DCM), which allows for inferences about the neuronal architectures that generate hemodynamic or electromagnetic signals (*17*, *18*). DCM uses a generative model of how electrophysiological signals are produced at the neuronal level; it employs neural mass models and Bayesian statistics to infer the neuronal mechanisms (effective connectivity) underlying observed evoked electrophysiological responses (*19*, *20*). This method has been validated in a

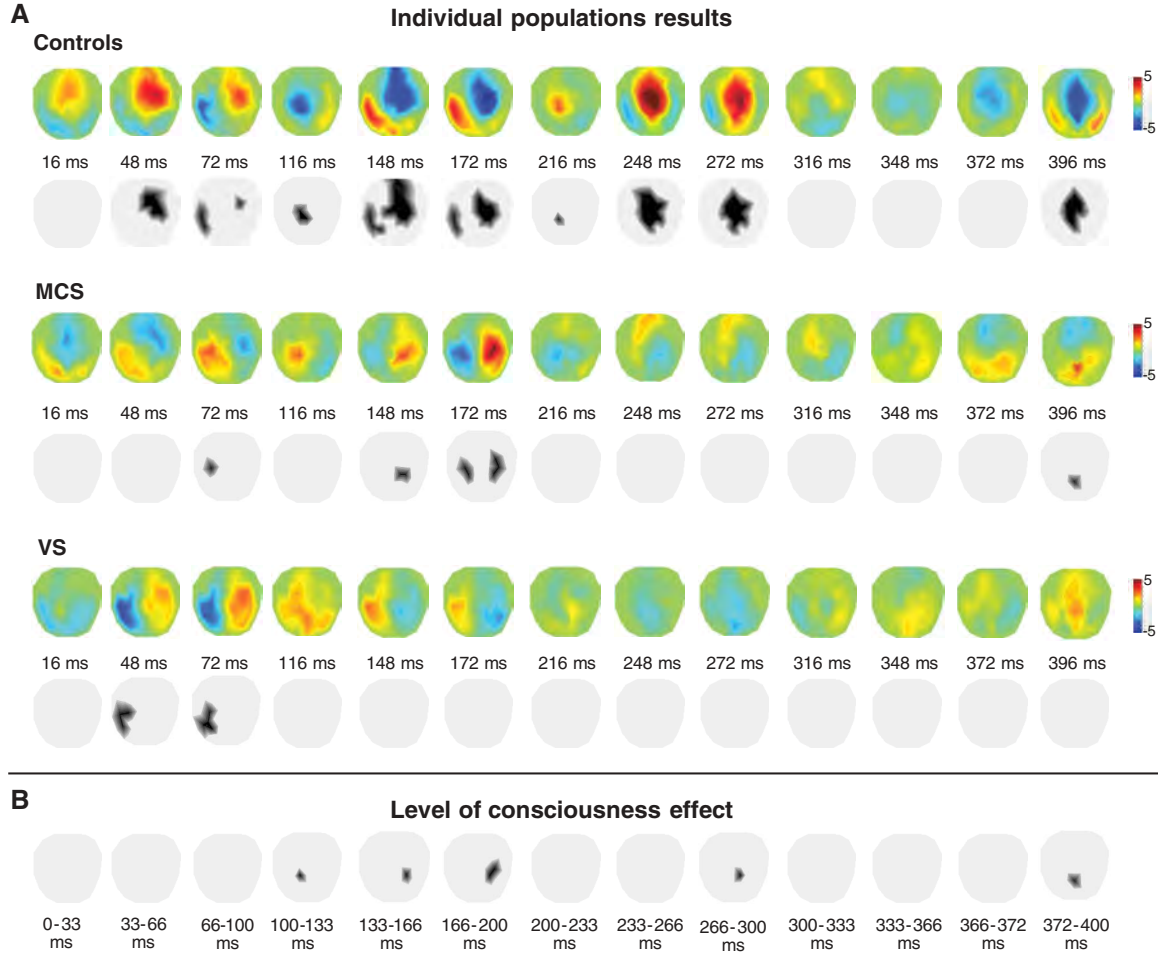


Fig. 2. Spatiotemporal grand-mean difference between standard and deviants correlates with the level of consciousness. The two-dimensional scalp topographies are interpolated from the 60 channels. (**A**) Statistical parametric maps of differential group responses in controls, MCS patients, and VS patients. For display purposes, instantaneous T maps are displayed without threshold and with threshold at $P < 0.001$ (uncorrected) in the three populations. Color scales correspond respectively to T values or to significant (in black) voxels. (**B**) Statistical parametric maps showing scalp regions where there is a significant interaction between response amplitude and consciousness level (with the threshold at $P < 0.05$; family-wise error corrected) over different time windows. Significant effects were found over temporal and frontal sensors in the range of 115 to 395 ms.

number of electrophysiological studies (*11*, *21*–*23*) and provides an efficient way to map from observed evoked potential patterns to causative neuronal mechanisms (*24*).

The present study used DCM of event-related potentials to quantify effective connectivity in backward and forward connections at two hierarchical cortical levels (i.e., in temporal and frontal cortices), during auditory processing in healthy subjects and MCS and VS patients. We used a roving oddball paradigm (Fig. 1), as in previous DCM studies (*22*, *23*) (SOM text). The functional anatomy engaged by this paradigm involves both forward and backward connections in a fronto-temporal cortical network (*22*). High-density ERP recordings were acquired in 21 brain-damaged patients (8 VS and 13 MCS) and 22 healthy controls (*25*). ERP data analysis, performed with statistical parametric mapping, tested the differential processing of standard and deviant sounds (*25*). Scalp-level group analyses detected long-latency components with a central topography in both controls and patients in a MCS ($P < 0.05$, family-wise error corrected). Peak latencies for the MMN were 170 ms in controls and 175 ms in patients in a MCS. Although the MMN was the most significant in MCS, the P3 component

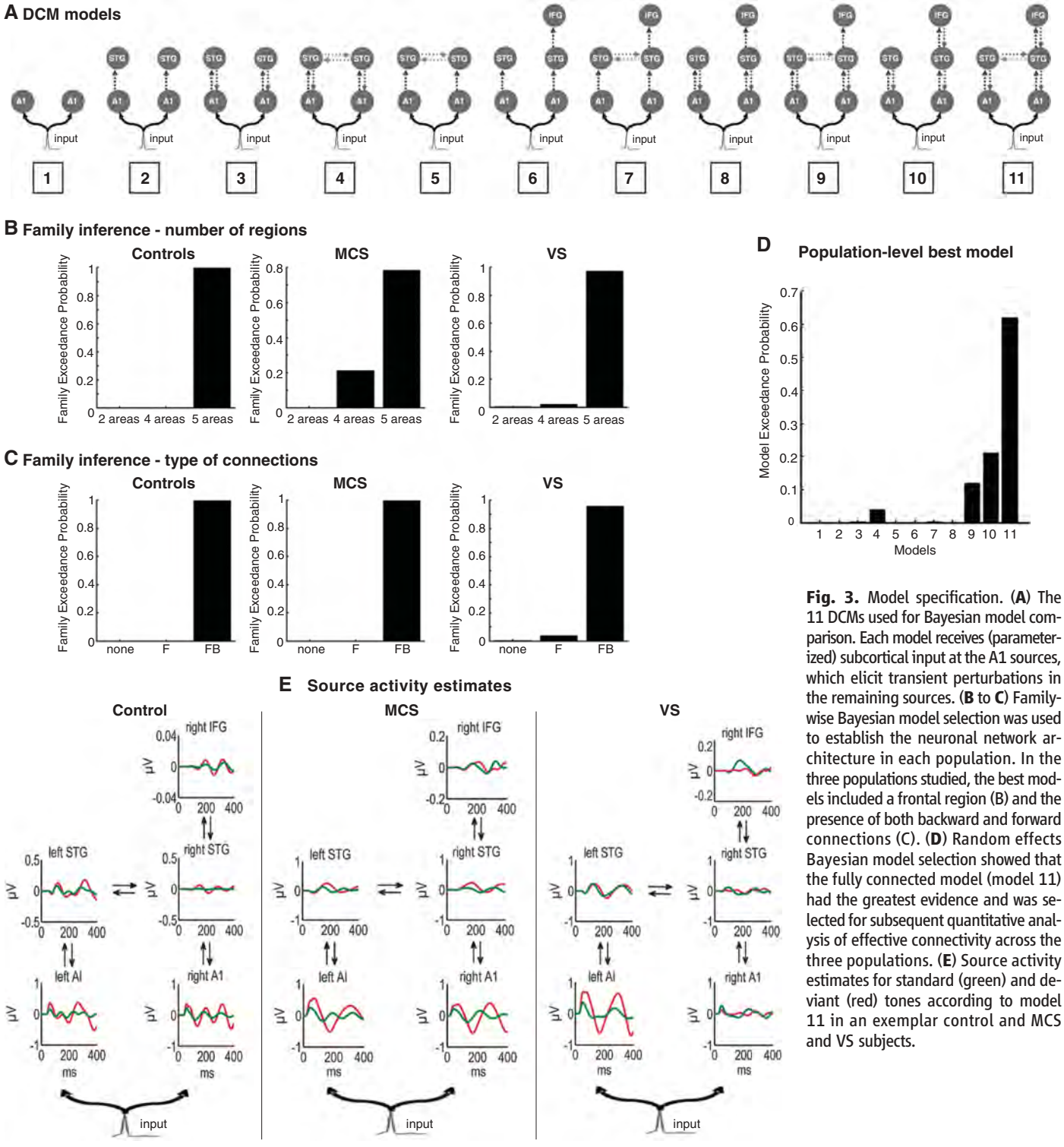


Fig. 3. Model specification. (**A**) The 11 DCMs used for Bayesian model comparison. Each model receives (parameterized) subcortical input at the A1 sources, which elicit transient perturbations in the remaining sources. (**B** to **C**) Family-wise Bayesian model selection was used to establish the neuronal network architecture in each population. In the three populations studied, the best models included a frontal region (B) and the presence of both backward and forward connections (C). (**D**) Random effects Bayesian model selection showed that the fully connected model (model 11) had the greatest evidence and was selected for subsequent quantitative analysis of effective connectivity across the three populations. (**E**) Source activity estimates for standard (green) and deviant (red) tones according to model 11 in an exemplar control and MCS and VS subjects.

(peak latency at 250 ms) was the most significant in controls. Only posterior early components (peak at 55 ms) could be seen in VS (Fig. 2). An analysis of covariance (ANCOVA) confirmed a significant interaction between level of consciousness and stimulus type on long-latency responses (peak latencies at 115, 175, 265, and 395 ms, $P < 0.05$, family-wise error corrected) across the three groups (Fig. 2).

Although the architecture of the network involved in the generation of MMN responses has been studied extensively in healthy volunteers (*26*) (SOM text), the involvement of frontal cortex, via its forward and backward connections, has yet to be established in brain-damaged patients. We thus performed a group-level Bayesian model comparison to identify the network architecture that best explained the responses of patients. Bayesian model selection (BMS) compared 11 models, which differed in the areas and connections involved (Fig. 3). Random effects family-level analysis showed that models including a frontal source with both forward and backward connections could best explain ERP responses in MCS and VS. For quantitative connectivity analysis, a second (random-effects) BMS procedure was applied to the 11 models, across all three groups (*25*). The fully connected model (model 11) had again the greatest evidence (Fig. 3). The corresponding source activity estimates in representative controls and MCS and VS subjects are also shown in Fig. 3. To assess differences between controls and patients, we compared the connectivity estimates (from the best model) using simple *t* tests (*25*). The only significant effect of the level of consciousness (differences between healthy volunteers, MCS subjects, and VS patient populations) was on the backward connection from frontal to superior temporal cortex (corrected $P = 0.012$), with no detectible differences in forward and backward processing in temporal cortex (Fig. 4). This backward connection was significantly impaired in VS patients as compared with controls ($P = 0.002$). MCS patients showed preserved top-down connectivity as compared with VS patients ($P = 0.001$) and were not significantly different from controls ($P > 0.05$) (Fig. 4).

Our main result is that, although the frontal cortex is still involved in the generation of the ERP in a VS, the main abnormality is in recurrent processing between higher-order cortices, owing to impaired backward connections from frontal to temporal cortices. Our analyses suggest that the (possibly diverse) pathophysiological causes of VS find a common expression in reducing top-down influences from frontal to temporal areas. Further research is required to establish the precise molecular or physiological mechanisms underlying these observations. In contrast to VS patients, MCS patients exhibited long-latency components in the scalp ERP and near-normal recurrent effective connectivity with higher-order cortices. This group difference cannot be attributable to differences in vigilance, as all patients were maintained in the same state of wakefulness throughout the experiment (*25*). Although forward connections are certainly needed for normal stimulus processing, these results suggest that the integrity of backward connections, or top-down processes, may be necessary for conscious perception. These findings stress the importance of recurrent processing in higher-order associative areas in the generation of conscious perception and do not support the view that recurrent processing in sensory cortex can be equated with consciousness (*27*). In contrast, our results suggest that recursive processing in high-order cortical areas is necessary for the generation of conscious perception (*5*). This would be mandated by the maintenance of high levels of integrated information, thought to be important for consciousness (*28*). A hierarchical recurrent cortical organization is also required by predictive coding formulations of the Bayesian brain hypothesis, which regards perception as inference on the causes of external stimuli (*29*). Under this perspective, VS patients are unable to elaborate (top-down) predictions of their sensorium, resulting (phenomenologically) in an impoverished percept and (physiologically) the absence of long-latency (endogenous) ERP components. Finally, our biologically plausible DCM shows that a selective impairment of a single (backward) connection accounts for widespread differences in the distributed responses we found between VS patients and healthy volunteers. This fits with the pervasive effects of recurrent processing on ERP amplitudes observed in healthy volunteers (a phenomenon referred to as "ignition") (*10*). Long-lasting slow ERP responses, such as K-complexes, can be observed during slow-wave sleep (*30*). Cortical connectivity analysis could be thus more specific than scalp-level analyses in terms of detecting the architectural correlates of conscious level. On the other hand, our analyses cannot say whether a failure of backward connectivity from the frontal region is a cause or consequence of processing that underlies consciousness (SOM text). What we can say is that a specific (top-down) failure of effective connectivity is implicated in consciousness and may play a necessary role.

In summary, our findings suggest that a selective disruption of top-down processes from high levels of a cortical hierarchy can lead to loss of consciousness in brain-damaged patients, and can clearly differentiate VS from MCS. In addition to its neuroscientific relevance, the present approach could constitute a new diagnostic tool to quantify the level of consciousness electrophysiologically at the patients' bedside. Further studies should also complement these findings in conditions such as sleep, epilepsy, or anesthesia-induced unconsciousness.

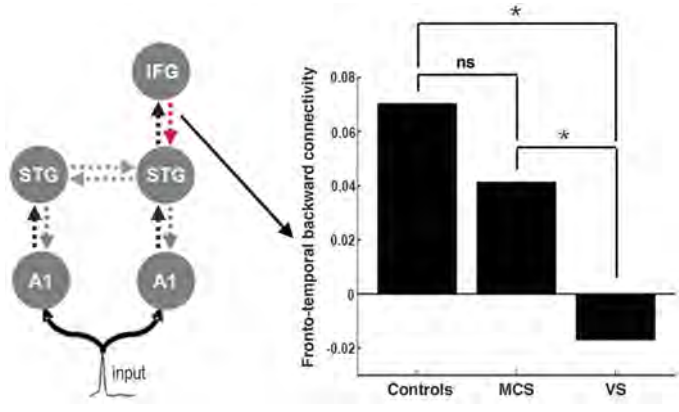


Fig. 4. Quantitative effective connectivity analysis revealed that the only significant difference between VS patients and controls was an impairment of backward connectivity from frontal to temporal cortex. MCS subjects showed significantly preserved connectivity compared with VS subjects and were not significantly different from controls.

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Response to Comment on "Preserved Feedforward But Impaired Top-Down Processes in the Vegetative State"

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King *et al*. raise some technical issues about our recent study showing impaired top-down processes in the vegetative state. We welcome the opportunity to provide more details about our methods and results and to resolve their concerns. We substantiate our interpretation of the results and provide a point-by-point response to the issues raised.

We thank King *et al*. (*1*) for deconstructing our paper (*2*) showing impaired top-down processes in the vegetative state (VS). We hope our responses provide some useful clarifications.

(i) Regarding the number of patients, it would have been disappointing not to have found a common abnormality in eight well-defined VS patients. If we had needed 50 patients to obtain significant differences, we would probably end up reporting quantitatively trivial effects that had little diagnostic value [a well-known fallacy of classical inference (*3*)]. We consider the heterogeneity as a strength of our cohort selection (*2*): We discovered a common mechanism underlying impaired consciousness, irrespective of its distal causes and subsequent clinical course. The ability to generalize our finding would have been compromised had we studied a more homogenous VS group.

(ii) Previous studies have provided inconsistent results concerning the presence of mismatch negativity (MMN) in VS. Faugeras *et al*. (*4*) did not investigate the presence of a MMN (local effect) but rather show a global effect in 2 VS patients out of 27. Bekinschtein *et al*. (*5*) studied only 4 VS patients and failed to detect a MMN in some. References (*6*, *7*) report considerable variability across studies, with a MMN in about 10 to 25% of patients. In short, a significant MMN, based on some threshold criteria, is not a generic characteristic of event-related potentials

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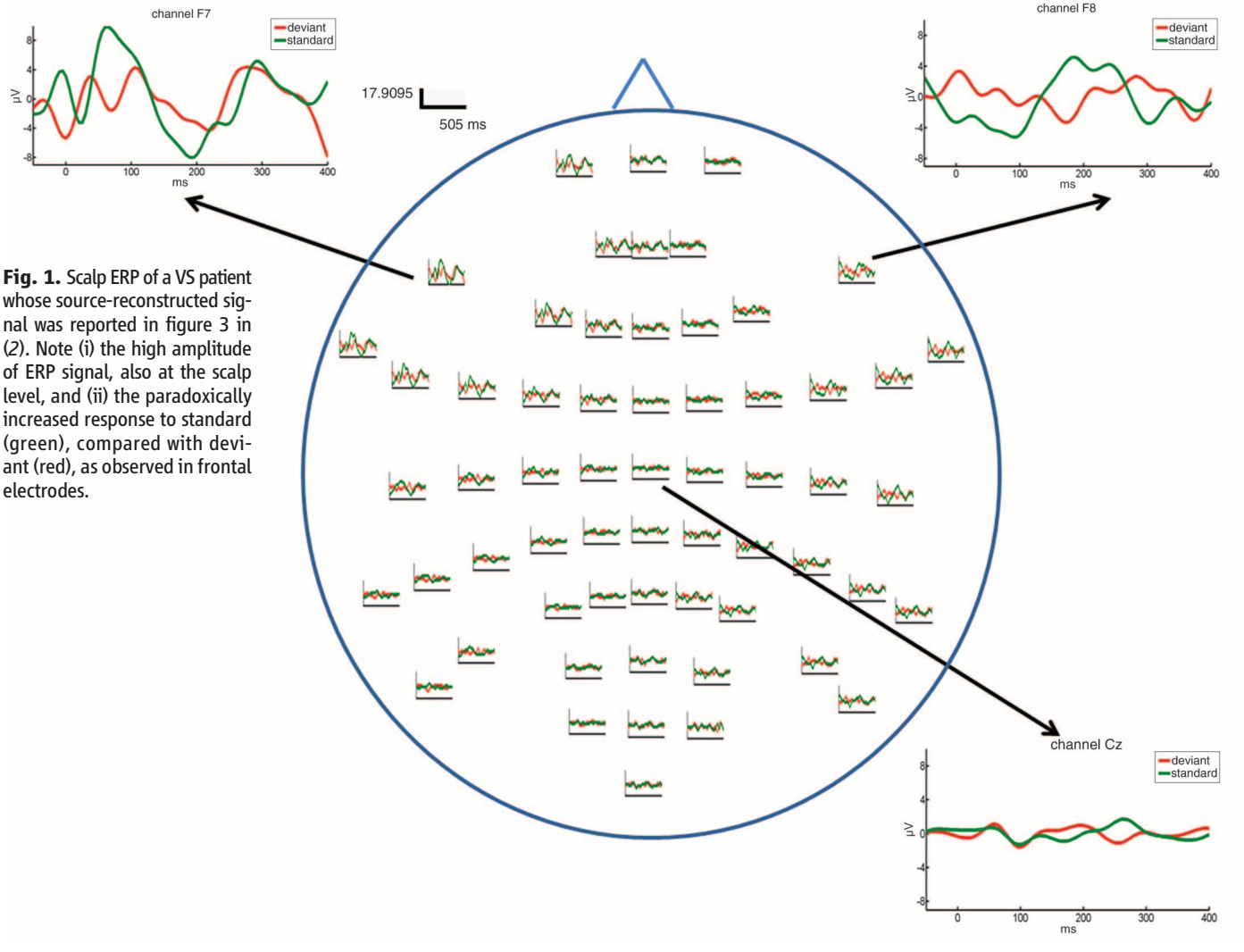


Fig. 1. Scalp ERP of a VS patient whose source-reconstructed signal was reported in figure 3 in (*2*). Note (i) the high amplitude of ERP signal, also at the scalp level, and (ii) the paradoxically increased response to standard (green), compared with deviant (red), as observed in frontal electrodes.

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(ERPs) in VS and is not a valid criterion for evaluating ERP data quality. Rather than assessing the presence of a threshold-based MMN, we examined correlations between ERP amplitude and the level of consciousness. We used a summary statistic (random effects) approach in all our analyses, ensuring that group results could not be explained by a strong effect in a minority of subjects (*8*).

(iii) With regard to ERP components and their latencies, we analyzed the whole peristimulus time window and indeed observed an ERP component corresponding to P50 in VS. We were not modeling the MMN per se (i.e., the difference waveform) but used the roving paradigm to characterize network responses to all stimuli. Waveform component latencies are defined using an ad hoc threshold on noisy time series, whereas dynamic causal modeling (DCM) looks for differences in the form of ERPs over all peristimulus time. To identify the MMN and reify it with a "latency" is not considered useful, necessary, or good practice in DCM.

(iv) It is not surprising that ERP topography is different in controls and VS patients, who are severely brain damaged. We used individual patient anatomy to account for possible differences in head conduction when performing DCM source reconstruction. Worries about signal-to-noise ratios can be discounted because differences were significant at the between-subject level using classical inference. If the data were just random fluctuations, these tests would not be significant. Differences between our data and King *et al*.'s results (*1*) might be due to differences in the stimuli [see (*9*)].

DCM source reconstruction provides a reasonable account of the scalp ERP data of the VS patient displayed in figure 3 in (*2*). In particular, the amplitudes of both scalp (Fig. 1) and source-reconstructed ERPs are bigger than typically observed in controls [figure 1 in (*2*)]. At both levels, the patient's frontal response to a "standard" is also bigger than the response to a "deviant." Merely observing ERP source reconstructions is insufficient to assert anything about backward versus forward connections; this is the role of DCM. To test models with and without laterality differences is another interesting issue, but not one that we have addressed.

(v) DCM implicit source reconstruction can efficiently reconstruct sources that are close together (*10*, *11*). Bayesian model selection (BMS) established that the use of five sources was the most appropriate for our data. ECD source reconstruction using 64 electrodes has been shown to be as accurate as an extended setup (*12*), especially when the data's signal-to-noise ratio is low (*13*). Finally, DCM uses the whole ERP time window to optimize its source reconstruction (*10*): Reconstructing only early components would not constitute a formal measure of inversion performance.

(vi) Our claim about preserved forward processes in VS was based on the involvement of frontal cortex in the generation of responses, as evidenced by BMS. At the level of quantitative parameter analyses, we can only reject the null hypothesis of no differences in the backward connections (because we used classical inference). This means that we can say nothing about the forward connections. We performed an additional analysis of variance for repeated measures, searching for an interaction between forward and backward frontotemporal connection strength in VS patients compared with controls. This interaction did not reach statistical significance ($P > 0.05$). A failure to demonstrate a significant difference can, however, not be taken as evidence for no difference (*2*). A BMS analysis on the VS subjects alone showed that model 9 (with preserved frontal forward connections but without backward connection) had more evidence than fully connected model 11 (with an 80% posterior confidence). Ideally, one would use BMS to ask about between-group differences in forward connections. However, hierarchical (between-subject) Bayesian models do not exist at present (for DCM).

Positron emission tomography measurements may fail to pick up the brief (subsecond) bottom-up afferents from auditory to frontal areas detected by ERP. Reduced frontal activation in VS could also reflect the pervasive effect of recurrent processing in the response to external stimuli (*14*). Several studies have established the importance of backward connections (*10*, *15*) and cognitive top-down processes (*16*) in long-latency component (such as P3) generation. An absence of P3 is therefore likely to reflect a disruption of backward rather than forward connections. It is probable that both forward and backward connections are important for consciousness. Our analysis suggests that backward connectivity from frontal to temporal cortex is the most consistent mechanistic abnormality underlying impaired consciousness in VS; however, this does not preclude a more widespread pathophysiology in any given patient.

We look forward to working with our peers to replicate our findings using other ERP paradigms. We would be glad to provide our help if needed.

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Supporting Online Material for

Preserved Feedforward but Impaired Top-Down Processes in the Vegetative State

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This PDF file includes

Materials and Methods
SOM Text
Fig. S1
Table S1
References

Supplementary methods

Patients

We compared 22 healthy volunteers (age range 20-81 years, mean age 37 ± SD 19 years, 7 males) with 21 brain damaged patients (13 MCS, 8 VS, age range 16-83 years, mean age 48 ± SD 20 years, 12 males). Patients' data are reported in the Supplementary Table. To ensure the generalizability of our results, we included patients with different etiologies and clinical histories, in the hope of finding a common deficit that underlies changes in conscious level, irrespective of its distal causes. Data were acquired in an un-sedated condition. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate in the study was obtained from the subjects themselves in the case of healthy subjects, and from the legal surrogate for the patients.

Behavioral assessments of consciousness were performed by trained and experienced neuropsychologists using the French adaptation of the Coma Recovery Scale-Revised (CRS-R) (*S1-2*) that has been specifically developed to disentangle VS from MCS patients but also MCS patients from patients who recovered their ability to communicate functionally (EMCS). The scale comprises six subscales: auditory, visual, motor and oromotor/verbal functions, as well as communication and level of arousal (see Supplementary Table for scores obtained by each patient in the CRS-R subscales). The 23 items are ordered according to their degree of complexity; the lowest item on each subscale represents reflexive activity, while the highest item represents behaviors that are cognitively mediated. Scoring is based on the presence or absence of operationally-defined behavioral responses to specific sensory stimuli (e.g., if visual pursuit of a mirror is present at least two times in the same direction, the patient is then considered to be MCS).

Data acquisition

We recorded auditory evoked potentials using a 60-channel EEG amplifier (Nexstim Ltd, Helsinki FI) (*S3*). To optimize signal quality, the impedance at all electrodes was kept below 5 kΩ. EEG signals were referenced to an additional electrode on the forehead, filtered (0.1-500 Hz) and sampled at 1450 Hz. Two extra sensors were used to record the electro-oculogram (EOG). To avoid a confounding effect due to differences in vigilance, arousal was maintained at a constant level throughout the experiment. During each EEG session, patients were lying on their beds, awake and with their eyes open. If signs of drowsiness appeared, recordings were momentarily interrupted and subjects were stimulated using the CRS-R arousal facilitation protocols. At the end of the experiment, the electrode positions and scalp landmarks (nasion, right and left tragus) were digitized.

Electroencephalographic activity was measured during an auditory roving 'oddball' paradigm (see Fig. 1A). The stimuli comprised a structured sequence of pure sinusoidal tones, with a roving, or sporadically changing tone. This paradigm is similar to that used in previous DCM studies investigating the functional architecture of mismatch negativity response (MMN) in healthy volunteers (*S4-5*). Within each stimulus train, all tones were of one frequency and were followed by a train of a different frequency. The first tone of a train was a deviant,

which eventually became a standard after few repetitions. This paradigm ensures that deviants and standards have exactly the same physical properties, differing only in the number of times they have been presented. This was varied pseudo-randomly between one and eleven. The probability that the same one was presented once or twice was 2.5%; for three and four times the probability was 3.75% and for five to eleven times it was 12.5%. The frequency of the tones varied from 500 to 800 Hz, in random steps with integer multiples of 50 Hz. Stimuli were presented binaurally via headphones for 15 min. The duration of each tone was 70 ms, with 5ms rise and fall times, and the inter-stimulus interval was 500 ms. About 250 deviant trials (first tone) and about 200 standards (eleventh tone) were presented to each subject. The loudness of the tones was set in each subject to a comfortable level, which was maintained throughout the experiment.

Data pre-processing and scalp level analysis

Pre-processing and data analysis were performed with SPM8 (http://www.fil.ion. ucl.ac.uk /spm/). The data were band-pass filtered between 0.5 and 20 Hz and down-sampled to 200 Hz. A correction for eye movements was performed (for each subject) using the Berg algorithm (*S6*) as implemented in SPM. The data were then epoched offline, with a peristimulus window of −100 to 400 ms. Artifacts were removed using robust averaging (*S4*), as described previously (*S7*). Averaged data were prepared for analysis using a second high-pass filtering at 20Hz and a correction for slow drifts via a third order discrete cosine transform procedure, as implemented in SPM. Trials were sorted in terms of tone repetition (*S4*). In other words, trials one to eleven corresponded to the responses elicited after one to eleven presentations of the same tone, collapsed across the whole range of frequencies. The first trail in each train (corresponding to the oddball or the deviant) and the eleventh (corresponding to the standard) were retained for further analysis. Data were transformed into scalp-map images (*S4*), which were then entered in a second level between-subjects random effects analysis. This used an ANCOVA model, with stimulus type (standard versus deviant) and the level of consciousness (3 levels: controls, MCS and VS) as factors. The different observations were assumed to be independent but their variances were assumed to be unequal. As previous studies (*S8-9*) show a correlation between mismatch negativity amplitude and prognosis, the patients' prognosis at 1 month were entered as a covariate of no interest (in VS patients: values of -2 if death, -1 if stay VS, 1 if evolution towards MCS; in MCS patients: -1 if stay MCS, 1 if emergence from MCS). F-contrasts were specified to test for differences between deviant and standard in controls, MCS and VS populations (simple effects of trial in each group). Finally, we used an F-contrast to search for the interaction with group; i.e., an ERP amplitude difference attributable to differences in the level of consciousness across the three populations. In all the SPM analyses, results were thresholded at p-value < 0.05, corrected for multiple comparisons using Random Field Theory in the usual way (*S10*). The peak latencies we refer to in the results are those of the local maxima of statistical significance of scalp-time group F-maps, as reported by SPM software.

The Supplementary Fig. shows instantaneous scalp T-maps over time, for the comparison standards versus deviants, in individual MCS and VS patients. These maps were obtained after filtering from 0.5 to 20 Hz, correction for eye movements using the Berg algorithm

described above, epoching from -100 to 400 ms, and correction of trials for slow drifts using a third order discrete cosine transform, as implemented in SPM. Individual epoched data were then converted to scalp-time images and a two sample T-test was performed, searching for a differential effect between standards and deviants in each patient. Scalp T-maps are displayed un-thresholded and at $p < 0.001$, uncorrected. In general, MCS patients show more robust differences at the individual level, although we did not obtain significant individual results in all patients. Note that the statistical criterion we used here is more conservative than commonly employed in ERP reports: a p-value threshold of 0.001 is equivalent to a correction for multiple comparisons over 50 time-points. The Supplementary Fig. also displays averaged ERP time courses in each MCS and VS patient. These were used for all our group analyses.

Dynamic causal modeling

Dynamic causal modeling (DCM) was originally developed for connectivity analysis of fMRI (*S11*) and M/EEG data (*S12*). Most approaches to connectivity analysis of M/EEG data use functional connectivity measures such as coherence or temporal correlations, which establish statistical dependencies between two time-series. However, there are certain cases where causal interactions are the focus of interest. In these situations, DCM is particularly useful, because it estimates effective connectivity (the influence one neuronal system has over another), under a perturbation, or stimulus. DCM models the interactions among cortical regions and allows one to make inferences about the parameters of that model and investigate how these parameters are influenced by experimental factors. DCM uses generative or forward models for evoked responses as measured with EEG/MEG (*S12-13*), and provides an important advance over conventional analyses of evoked responses because it places biophysically plausible constraints on the inversion; namely, activity in one source has to be caused by activity in another. DCMs for MEG/EEG use neural mass models (*S14*) to explain source activity in terms of the ensemble dynamics of interacting inhibitory and excitatory subpopulations of neurons, based on the model of Jansen and Rit (*S15*). The active sources are interconnected according to the connectivity rules described in (*S16*) and conform to a hierarchical model of intrinsic and extrinsic connections within and among multiple sources as described in (*S17*) and (*S18*). By taking the marginal likelihood over the conditional density of the model parameters, one can estimate the probability of the data, given a particular model. This is known as the marginal likelihood or evidence and can be used to compare and select the best model amongst alternative models. We have previously used DCM to explain ERPs to standards and deviants using a classical (*S19*) and roving paradigm (*S4-5*). Differences in the ERP to standards and deviants were modeled in terms of changes in synaptic connections within and between hierarchically organized cortical sources. Model comparison addressed hierarchical implementations of multiple-level network models ranging from one to three levels. These models allowed for changes in extrinsic connections in combination with changes in intrinsic connections at the different levels of the cortical hierarchy.

Model specification

DCM is usually used in a hypothesis-driven fashion: it does not explore all possible models but tests specific mechanistic hypotheses. Our models attempt to explain the generation of each individual response (i.e., responses to each tone presentation). Therefore, left and right A1 were chosen as cortical input stations for processing the auditory information. Doeller et al. (*S20*) identified sources for the differential response, with fMRI and EEG measures, in both left and right superior temporal gyrus (STG) and inferior frontal gyrus (IFG). Here, we modeled each active source; i.e., each node in the network, with a single equivalent current dipole (ECD) in a conventional electromagnetic forward model. This electromagnetic model used boundary element head models (*S21*), with homogeneous and isotropic conductivity as an approximation to the brain, cerebrospinal fluid (CSF), skull and scalp surfaces. Subject-specific head models were obtained using an inverse spatial normalization of a canonical mesh for each subject. Normalization parameters were obtained using unified segmentation of the subjects' structural images (computerized tomography or T1 MRI) as implemented in the SPM software. Coregistration of electrode position and head model was performed in each subject, prior to forward model computation. After the forward model was computed for each subject, the lead-field mapping cortical sources onto measured signals was parameterized in terms of the location and orientation of each dipole source in the DCM (*S4*). The coordinates reported by Opitz et al. (*S22*) (for STG and IFG) and Rademacher et al. (*S23*) (for left and right primary auditory cortex, A1) were chosen as prior source location means, with a prior variance of $16mm^2$.We converted these coordinates, given in the literature in Talairach space, to MNI space using the algorithm described in http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach. The moment parameters had prior mean of zero and a variance of 256 mm^2 in each direction. This is equivalent to assuming uninformative or flat priors on the orientations of the dipole moments. For computational expediency, DCMs (see below) were computed on a reduced form of data that corresponded to eight channel mixtures or spatial modes. These were the eight principal modes of a singular value decomposition (SVD) of the channel data between 0 and 400 ms, over the trial types of interest. These were the standard and deviant trials above.

DCMs

Bayesian model selection considered eleven models specified by their architecture (see Fig. 3). These models covered different levels of hierarchical complexity, both in terms of the number of areas involved, and the extrinsic (between-source) connections. The models started with the most parsimonious model, Model 1 (a one-level hierarchical model comprising two nodes in the left and right A1) and increased in their complexity, in terms of hierarchical levels, number of sources and extrinsic connections. The inclusion of nodes and connections to the initial model culminated in a non-symmetric three-level hierarchical model that included bilateral A1 and STG, and right IFG. All models can therefore be considered as a sub-model of the last one, Model 11. Our simplest model, Model 1, is a two source network corresponding to the hypothesis that the ERPs are generated by bilateral activity in A1. Models 2 to 5 build on Model 1 through addition of left and right STG sources (connected

through forward connections to ipsilateral A1, and in more complex models through backward connections to ipsilateral A1, and/or via lateral connections with each other). A third-level family of models, Models 6 to 11, comprising five sources, included a right IFG source. Right STG was connected with ipsilateral IFG. Models 6 to 11 differ in the successive addition of backward and lateral connections at different levels of the cortical hierarchy. We accommodated differences in the ERP to standard and deviants by condition-specific scaling parameters on every connection in each model. This meant that Models 2 to 11 cover the hypotheses that both local adaptation (*S24*), within each area, and interactions within a temporo-frontal network (*S25-26*) underlie the generation of the MMN.

Statistical analysis

Statistical analyses in this paper were based on a two-stage (summary-statistic) approach. In a first stage, Bayesian model comparison was used to optimize the network architecture (DCM) underlying electrophysiological responses to auditory stimulation in controls, MCS and VS patients. In a second stage, a quantitative connectivity analysis was performed, conditioned upon the winning model, searching for differences in connectivity between controls, MCS and VS patients, in response to auditory stimulation. The second stage used the conditional (within-subject) estimates of effective connections from the winning DCM as the dependent variable in a classical (between-subject) ANOVA.

Bayesian model selection (BMS)

DCM inversion involves optimizing a model (m) which provides two important quantities: the free-energy bound on the model-evidence $p(y|m)$, used for model comparison, and the posterior or conditional density of the model parameters, $p(\theta|y,m)$. Specifically, inversion of a DCM corresponds to approximating the posterior probability of the parameters using variational Bayes (*S27*). The aim is to minimize a free-energy bound on the log-evidence, with respect to a variational density, $q(\theta)$. When the free-energy is minimized; $q(\theta)=p(\theta|y,m)$ and the free-energy $F = -\ln p(y|m)$ approximates the negative marginal log-likelihood or negative log-evidence. After convergence, the variational density is used as an approximation to the desired conditional density and the log-evidence is used for model comparison.
One often wants to compare different models and select the best before making statistical inferences on the basis of the conditional density (see above). The best model, given the data, is the one with the highest log-evidence, $\ln p(y|m)$ (assuming a uniform prior over models). Given two models m_1 and m_2 one can compare them by computing their relative log-evidence $\ln p(y|m_1) - \ln p(y|m_2)$ (*S4*). One may wish to select the model that best explains multiple data sets, i.e., the best model at the group level. Alternatively, we can make inferences about general characteristics of model architecture using family-based inferences, which compare different groups of models characterized by similar architectural properties (*S28*). We thus performed family-wise inferences in each population, using a random effects approach, which is robust to potential outliers in the population (*S29*). A first family-wise inference optimized the number of areas that explained the data of the three populations. We separated the model space into three families: two-area models with bilateral A1 only (Model 1); four-area models

with bilateral A1 and STG (Models 2 to 5), and five-area models with bilateral A1 and STG, and right IFG (Models 6 to 11). Bayesian model selection showed that the five-area models were the best. A second family-wise inference addressed the connectivity architecture. Three families were considered: models with no inter-areal connections (Model 1), models with forward connections only (Models 2, 5, 6 and 7), and models with both forward and backward connections (Models 3, 4, 8, 9, 10 and 11). This BMS procedure established the presence of recurrent connections, involving the prefrontal source, and demonstrates the consistency of BMS over the three groups of subjects (Fig. 3 – left panel). The superiority of the full model (model 11) was confirmed with an exhaustive model search over all models using a (random effects) BMS over all subjects (Fig. 3 – right panel). Fig. 3 (lower panel) displays source activity estimates in representative subjects according to this model. These predictions of source activity over time illustrate the preservation of frontal responsiveness in MCS as in VS patients.

Quantitative connectivity analysis

We used the winning model above for final (between-subject) statistical analysis of the conditional estimates of connectivity. In our DCMs, the effects of deviant stimuli (relative to standards) are modeled by scaling the effective connectivity in a trial-specific fashion. Although we tested for group differences in this (MMN-related) scaling, our primary interest was in differences in the underlying connection strengths mediated distributed responses to all stimuli. We exported the connectivity estimates to SPSS, and performed an ANCOVA, using the patients' prognosis as a covariate of no interest (as defined above). We tested each forward and backward connection independently with appropriate contrasts. We first searched for an effect of the level of consciousness on changes in connectivity between standard and deviants. We then tested for group differences in connection strength *per se*. We found a significant difference in the backward connection between frontal and temporal cortices between controls, MCS and VS, at $p < 0.05$, corrected for multiple comparisons using Bonferroni procedure; i.e., taking into account the number of connections tested.

Supplementary discussion

Previous literature on MMN in healthy volunteers

There is a large literature validating DCM for electrophysiological responses that uses both psychological (*S4, S18-19, S30-38*) and psychopharmacological (*S39-40*) constructs. The choice of the mismatch negativity paradigm in the current study was based on several years of experience with this paradigm and its modeling (with both DCM (*S4, S18-19, S31-32, S41*) and neuronal simulations (*S18, S42*)). In short, we chose the mismatch negativity paradigm not only because it was particularly appropriate for the patients we studied but because we have a wealth of information about the underlying mechanisms and networks from lesions studies (e.g. (*S43-44*)), fMRI studies of normal subjects (e.g. (*S20, S22, S45*)), high-density EEG (e.g. (*S46-48*)) and MEG studies (e.g. (*S48-50*)). The five area model we used, including a right frontal region (*S22, S46*) has been shown to have the greatest evidence in a number of

DCM studies; using different variants of the MMN paradigm and different subjects (*S4, S18-19, S31-32, S41*).

Previous MMN studies in MCS and VS patients

Previous studies have used auditory event-related potentials to assess prognosis in severely brain-damaged patients. The presence of MMN is a good predictor of awakening and suggests that comatose patients will not enter a permanent vegetative state (*S8, S51-57*). In contrast, only a few studies have investigated the correlation between MMN and level of consciousness. A study by Wijnen and collaborators (*S9*) showed that the amplitude of the MMN increases with recovery from VS to normal consciousness. This study found a significant correlation between the amplitude of the MMN and level of consciousness, when comparing VS with MCS and subsequent emergence from MCS (*S9*). A recent study by Fischer and collaborators (*S58*) failed to replicate these results. However, one might argue that a failure to demonstrate MMN differences does not mean they do not exist (classical statistics control type I, not type II errors). While Wijnen's analysis and our study investigated between-condition differences in MMN amplitude, Fischer et al. used an all-or-none (based on some threshold) MMN scoring procedure in individual brain-damaged patients. Finally, these differences may also speak to the distinction between phenomenological (MMN) differences in observed scalp-level responses (in data-space) and a (possibly more sensitive) comparison of their underlying causes (e.g., coupling strengths – see also discussion below).

Technical comments

DCM does not examine coupling among sources following the inversion of a classical electromagnetic forward model. It subsumes the inversion of a classical model and tries to explain the data as observed in channel-space. In other words, DCM is a generalization of classical inversion schemes, not an add-on. The parameters estimated from the DCM and the evaluation of the DCMs per se were based on exactly the same (ERP) data. The SPM (scalp-level) analyses report classical inferences on responses over channels and peristimulus time. They represent a statement about phenomena observed in data-space. Conversely, the DCM analyses pertain to the underlying causes of these phenomena and their group differences. These causes include the hidden source activity and coupling parameters. The parameters of the network (DCM) are estimates of the functional architectures producing observed differences. Group comparisons of these parameter estimates (using simple classical inference) allow one to interpret scalp-level differences mechanistically, by appealing to the neurobiologically grounded DCM. Discrepancies between these complementary (SPM and DCM) analyses are resolved easily by noting that a failure to demonstrate a significant difference cannot be taken as evidence for no difference.

It is important to note that the inference about impaired connectivity was direct and based upon simple classical tests (T-tests). This pre-empts any concerns about the robustness or sensitivity of DCM. Put simply, DCM was used to furnish quantities (coupling parameters) that could be interpreted in relation to an underlying model. However, the inference about these quantities was based upon straightforward classical statistics which, under the null

hypothesis of no differences, could not have given significant results. The fact that we obtained selective and significant results could be construed as a validation of the DCM; in the sense that it parameterized something that differed significantly between the groups.

At a conceptual level, the model employed here considers the regions involved in the generation of the individual responses in isolation. However, in EEG some nonspecific state variables can have a systematic effect on stimulus processing, and also on the emergence of a conscious experience. An example of this is provided by studies showing that the conscious visual perception depends on the level of occipital alpha (*S59*). Conversely, both sensory stimuli and attention may affect physiological states. In short one cannot ignore interactions among brain state, stimulus processing and conscious awareness. In our patients, the classical EEG markers of brain state were drastically altered. However, it is difficult to be definitive about what causes what. In other words, perceptual processing can cause a change in synaptic coupling, which changes the nature of perceptual processing. A simple example here might be attentional increases in postsynaptic gain (mediated by activity-dependent changes in synaptic efficacy) (*S60*). In our context, this means that a failure of backward connectivity from the frontal region may be a cause or consequence of processing that underlies consciousness. We deliberately chose the mismatch negativity paradigm because it elicits well characterized electrophysiological responses even in the absence of attention and (perhaps) explicit awareness (*S68*). These responses enable us to estimate the underlying network and distributed processing using DCM. However, there is no supposition that the responses elicited in this paradigm are related to the perception of the stimuli used. Associating changes in backward connections from the frontal cortex with conscious perception is based purely upon the fact that it is changes in these and only these connections that are common to patients that show deficits of perceptual awareness. In short, the key experimental manipulation here was not the standard or deviant stimuli of the mismatch negativity paradigm but the selection of subjects with different levels of consciousness. This allowed us to detect changes in network architecture that are related not to the content (perception of a particular sound), but to the level of consciousness. This approach is used in studies correlating the mismatch negativity component with the level of consciousness during anesthesia (*S61*) and sleep (*S62*). It is also adopted in experiments using transcranial magnetic stimulation (TMS) (*S63-65*): perturbing the system with TMS allows one to characterize network changes underlying various levels of consciousness (*S66-67*). In short, we were able to establish that a failure of backward effective connectivity is associated with decreased level of consciousness. This failure may or may not be necessary to explain any abnormal perceptual content elicited by the standard and oddball stimuli in our paradigm.

Finally, it would be interesting to determine which EEG frequencies contribute to the interactions among sources. In particular, do long-distance backward fronto-temporal connections employ beta-band frequencies or slower (alpha band) or faster dynamics (gamma band)? As fast rhythms like gamma are prone to corruption by non-neuronal noise in scalp-level EEG recordings (*S69*), the use of invasive electrophysiological data may be more suited to answer this question. To address this issue, one could use DCM for induced responses (*S35*). DCM for ERP, as used here, tries to explain evoked as opposed to induced responses. This means that the differences in coupling explain only the evoked data features and do not explain any induced components. It may be that effective connectivity depends upon (or is

changed by) high frequency synchronous activity (e.g., communication through coherence or synchronous gain (*S60*, *S70*)). In a DCM for ERP (as used here) this would be expressed as increased effective connectivity, provided induced responses are expressed consistently in peristimulus time. To understand the relationship between how different data features (e.g., evoked versus induced) are caused one would have to model both explicitly. DCM for induced responses may provide a more rounded picture on what aspects of brain dynamics mediate the coupling between brain regions and the aberrant coupling reported here.

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Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state

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Summary

Monitoring the level of consciousness in brain injured patients with disorders of consciousness is crucial as it provides diagnostic and prognostic information. Behavioral assessment remains the gold standard for assessing consciousness but previous studies have shown a high rate of misdiagnosis. This study aimed to investigate the usefulness of electroencephalography (EEG) entropy measurements in differentiating unconscious (coma or vegetative) from minimally conscious patients.
Left fronto-temporal EEG recordings (10-minute resting state epochs) were prospectively obtained in 56 patients and 16 age-matched healthy volunteers. Patients were assessed in the acute (≤1 month post-injury; n=29) or chronic (>1 month post-injury; n=27) stage. The etiology was traumatic in 23 patients. Automated online EEG entropy calculations (providing an arbitrary value ranging from 0 to 91) were compared with behavioral assessments (Coma Recovery Scale-Revised) and outcome.
EEG entropy correlated with Coma Recovery Scale total scores (r=0.49). Mean EEG entropy values were higher in minimally conscious (73±19; mean and standard deviation) than in vegetative/unresponsive wakefulness syndrome patients (45±28). Receiver operating characteristic analysis revealed an entropy cut-off value of 52 differentiating acute unconscious from minimally conscious patients (sensitivity 89% and specificity 90%). In chronic patients, entropy measurements offered no reliable diagnostic information. EEG entropy measurements did not allow prediction of outcome.
User-independent time-frequency balanced spectral EEG entropy measurements seem to constitute an interesting diagnostic – albeit not prognostic – tool for assessing neural network complexity in disorders of consciousness in the acute setting. Future studies are needed before using this tool in routine clinical practice, and these should seek to improve automated EEG quantification paradigms in order to reduce the remaining false negative and false positive findings.

KEY WORDS: coma, EEG entropy, electroencephalography, minimally conscious state, unresponsive wakefulness syndrome, vegetative state

Introduction

Distinguishing, after a severe acquired brain injury, between unconscious comatose or vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients and conscious or minimally conscious state (MCS) patients [1] remains extremely challenging. Coma is defined by the absence of both arousal (i.e., absence of eye opening) and awareness (i.e., absence of voluntary or non-reflex movements) [2]. VS/UWS is characterized by the return of arousal without recovery of awareness. The MCS is defined by the presence of inconsistent but reproducible goal-directed behaviors (e.g., response to command, visual pursuit, localization of noxious stimulations or contingent behavior in response to specific emotional stimuli) [3]. Patients with such disorders of consciousness (DOC) who remain unable to communicate represent a major diagnostic challenge [4]. Assessing the level and content of consciousness is indeed intrinsically difficult. Voluntary movements are easily misinterpreted as reflex activity and motor responses may be very limited or easily exhausted due to fluctuating vigilance [5]. Studies have shown that up to 40% of patients diagnosed as unconscious or vegetative may show signs of consciousness when assessed with standardized behavioral scales [6-9]. The Coma Recovery Scale-Revised (CRS-R) has been developed specifically to differentiate MCS from VS/UWS patients [10]. However, these evaluations require time and trained, experienced

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assessors. The aim of this study was to investigate the usefulness of automated electroencephalography (EEG) entropy measurements in the differential diagnosis of DOC.

The EEG is an objective tool that permits continuous and online monitoring of brain function. Since interpretation of the raw EEG signal requires considerable expertise and specialized training, simpler and more standardized measures of brain function are desired [11]. Originating from thermodynamics, EEG entropy is a measure of disorder that describes the irregularity, complexity, or unpredictability of a stochastic EEG signal [12]. A regular EEG signal, such as the one recorded in slow wave sleep or deep anesthesia, has very low entropy while the multitude of brain activities of an awake subject generates a more complex signal (i.e., with high entropy). Entropy is known to be independent of absolute scales such as the amplitude or the frequency of the signal [13] and can be calculated in several ways. Approximate entropy [14,15] or Shannon entropy [16,17] analyses the time domain, whereas spectral entropy [18,19] assesses the frequency domain. Here we used an automated time-frequency balanced spectral entropy device previously validated for monitoring the level of general anesthesia in patients undergoing surgery [20-22]. To date, however, no studies have assessed its sensitivity and specificity in the diagnosis and prognosis of DOC.

Materials and methods

This multicentric study was prospectively performed in 56 patients with DOC who were comatose on admission (aged 54±19 years; 37 males) and in 16 age-matched healthy participants without a neurological or neurosurgical history (50±17 years; 9 males). Inclusion criteria for patients included: age over 18 years; no neurological or neurosurgical history other than the brain injury; absence of centrally-acting drugs or neuromuscular function blockers; diagnosis, according to the international criteria, of: coma [2], VS/UWS [1,23] or MCS [3] caused by acute acquired brain damage (traumatic or non-traumatic). Assessment of functional outcome was performed at one-year follow up. The study was approved by the ethics committees of the Faculties of Medicine of the Universities of Liège and Brussels. Written informed consent was obtained from all the control subjects and from the patients' legal surrogates.

Behavioral measurements of consciousness were obtained by trained, experienced neuropsychologists using the French adaptation of the Coma Recovery Scale-Revised (CRS-R) [10,24]. The CRS-R consists of six subscales: auditory, visual, motor and oromotor/verbal functions as well as communication and level of arousal. The 23 items are ordered according to their degree of complexity; the lowest item on each subscale represents reflexive activity while the highest item represents behaviors that are cognitively mediated. Scoring is based on the presence or absence of operationally-defined behavioral responses to specific sensory stimuli (e.g. if visual pursuit of a mirror is present at least twice in the same direction, the patient is considered to be in the MCS).

EEG recordings (10-minute epochs) during the resting state were obtained following the arousal facilitation protocol as defined in the CRS-R manual [10,24]. After skin preparation with isopropyl alcohol, specific entropy sensors (Datex-Ohmeda S/5, GE Healthcare, Datex-Ohmeda Division, Helsinki, Finland), composed of self-adhering flexible bands holding three electrodes, were placed on the forehead and temple. Impedances were kept <5 kΩ and data were sampled at 400Hz. Online state entropy and response entropy were recorded on a portable computer using the Datex-Ohmeda Collect S/5 software. The monitor automatically recorded two kinds of entropy: state entropy (only cortical EEG) and response entropy (also including frontal electromyogram). The difference between state and response entropy is that the latter is more influenced by the contribution from the electromyography-dominated high-frequency band [25]. State entropy was calculated over the EEG dominant frequency range from 0.8 to 32Hz and response entropy was measured over the complete range of frequencies from 0.8 to 47Hz. Note that state entropy parameters can vary from 0 (suppression of EEG) to 91 (alertness), whereas response entropy ranges from 0 to 100.

The basis of the Datex-Ohmeda entropy algorithm is *time-frequency balanced spectral entropy* which is computed from a time-frequency decomposition of the signal. The signal is decomposed in its different frequencies and each frequency is computed not once but with a sliding window whose size depends on the frequency. The decomposition is dependent on the frequency of the signal: low frequency (needing more signal) will be assessed using a larger window as compared to high frequency. For each time interval (i.e., 1 second) a spectral entropy is automatically computed [21].

Statistical analyses were performed using STATA software (Stata Statistical Software; Release 11. College Station, TX: StataCorp LP 2009). Correlation analysis between behavioral scales (CRS-R total score) and EEG entropy was performed using Spearman testing. Non-parametric tests were used for univariate analysis (Wilcoxon rank sum/Mann-Whitney test and Kruskal-Wallis test) to test whether EEG entropy differed i) between diagnostic groups, ii) between acute and chronic patients, and iii) according to etiology (traumatic vs non-traumatic). Multivariate analyses were also performed using the logistic regression model. Receiver operating characteristic (ROC) analysis [26] was used to identify a cut-off value differentiating conscious (MCS) from unconscious (coma or VS/UWS) patients and to differentiate good (i.e., recovery of functional communication) from bad outcome. Results were considered significant at $p<0.05$.

Results

Fifty-six patients and 16 age-matched healthy volunteers were enrolled in this study. Etiology was traumatic in 23 patients; the non-traumatic cases (n=33) comprised patients with post-anoxic-ischemic encephalopathy (n=16), ischemic or hemorrhagic stroke (n=10), subarachnoid hemorrhage (n=3), encephalitis (n=2) and metabolic encephalopathies (n=2). Patients were assessed in the acute (≤1 month post-injury; n=29) or chronic (>1 month post-injury; n=27) stages. The acute patients had the following clinical diagnoses: coma (n=6; mean CRS-R total score of 1±1); VS/UWS (n=14;

CRS-R total score of 4±1) and MCS (n=9; CRS-R total score of 11±3); the chronic patients were diagnosed with: VS/UWS (n=10; CRS-R total score of 5±1) and MCS (n=17; CRS-R total score of 11±4).

In the 56 patients with DOC, mean resting state EEG entropy measurements showed a positive linear correlation with CRS-R total scores ($r=0.49$; $p<0.001$) (Fig. 1). The patients' mean EEG entropy values differed between diagnostic groups (35±28 in coma; 45±28 in VS/UWS and 73±19 in MCS; $Chi^2 = 31.97$; $p<0.001$). The healthy controls showed mean entropy values of 89±1. The MCS patients showed higher EEG entropy values than the VS/UWS patients ($Z=-2.95$; $p=0.003$). EEG entropy values also differed between acute and chronic patients (43±24 versus 73±25 respectively; $Z=-4.2$; $p<0.001$). No differences were observed between traumatic and non-traumatic etiology (61±28 versus 54±28 respectively; $Z=-0.84$; $p=0.4$). Figure 2 shows the entropy values in acute (coma, VS/UWS, MCS) and chronic (VS/UWS, MCS) patients, and in healthy volunteers.

ROC analysis revealed an entropy cut-off value of 67 differentiating unconscious (coma, VS/UWS) from conscious patients (MCS), with a sensitivity and a specificity of 77% (area under the curve 0.8; 95% confidence interval 0.6-0.9). Likewise, in the acute patients, ROC analysis identified a cut-off value of 52 differentiating unconscious from conscious patients, giving a sensitivity of 89% and a specificity of 90% (area under the curve 0.9; 95% confidence interval 0.8-1.00). In the chronic patients, on the other hand, the sensitivity and specificity of the ROC analysis was too low to allow reliable conclusions to be drawn (area under the curve 0.5; 95% confidence interval 0.3-0.8).

At one-year follow up it was found that of the 56 studied patients, 24 had died, five were still classifiable as VS/UWS, 17 showed a severe disability, three showed a moderate disability, and four had returned to independent living (missing data: n=2). Initial EEG entropy values did not predict patients with good or poor outcome

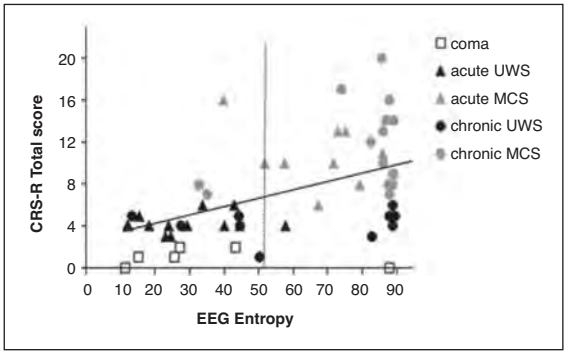


Figure 1 - Correlation between EEG entropy and Coma Recovery Scale–Revised (CRS-R) behavioral assessments in coma (white squares), acute unresponsive wakefulness syndrome (UWS; black triangles), chronic UWS (black circles), acute minimally conscious state (MCS; grey triangles) and chronic MCS (grey circles). The dashed line shows the EEG entropy cut-off value of 52, separating conscious from unconscious patients. Note that a positive linear correlation between EEG entropy and CRS-R total scores was observed: the higher the EEG entropy value, the higher the level of consciousness. Note also that false positives occurred mainly in chronic cases.

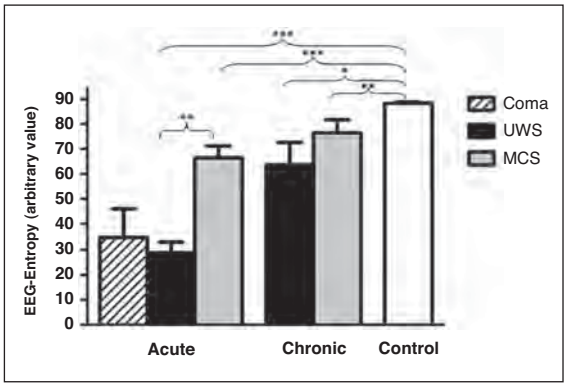


Figure 2 - EEG entropy values in acute and chronic disorders of consciousness, and healthy volunteers. (*=p<0.05; **=p<0.001; ***p<0.0001). Mean EEG entropy values are different between groups. In the acute group, MCS patients showed higher EEG entropy values than VS/UWS patients.

(57±29 versus 57±25 respectively; $p=0.72$). In the acute setting, ROC analysis differentiating poor from good outcome identified a cut-off entropy value of 57 with a specificity of 78% and a sensitivity of 60% (area under the curve 0.70; 95% confidence interval 0.4-0.9). The observed area under the ROC curve (0.70) is considered to reflect a moderate discrimination capacity and means that in patients with an entropy value above 57, the test will correctly recognize 60% of those who will recover and 78% of those who will not recover functional communication (i.e., emerge from MCS) one year later. For chronic patients, the prognostic value of the entropy measurements was shown to be of even lower than for acute patients.

Similar results were obtained for all reported analyses when using response entropy variables as opposed to the reported state entropy variables.

Discussion

Electroencephalography can be used to assess thalamocortical function in severe brain damage and can help to establish the prognosis of patients still in the acute stage, especially those in anoxic comatose states [11,27-29]. The diagnostic use of EEG in DOC, on the other hand, is less documented [30]. Previous studies employing automated user-independent EEG quantification correlated the EEG bispectral index (BIS) with clinical assessment and outcome [31-33]. Similar to EEG entropy calculation, the EEG BIS is primarily used and validated as a means of monitoring the degree of sedation during anesthesia [34,35] and it ranges from 0 (death) to 100 (fully awake) [36]. A disadvantage of bispectral monitoring is that the calculation parameters used (i.e., frequency analysis or the ratio of the power in the high and low beta ranges; bispectral analysis or the ratio of the bicoherence in fast and slower frequencies; and time domain analysis or burst suppression ratio) remain hidden, which makes it a "black box", not appreciated by electrophysiologists and neurologists, and not acceptable for scientific measurements. In this study, we therefore focused on EEG entropy measurements as a

means of assessing the level of consciousness in DOC. The automated time-frequency balanced spectral entropy measurements used in this study (combining both time and frequency domains) were shown to correlate with behavioral assessments of consciousness as measured by the CRS-R total score. This finding extends preliminary data showing a correlation between EEG approximate entropy offline calculations and the less sensitive Glasgow Coma Scale in coma survivors [37]. The online-calculated state entropy values of our VS/UWS and MCS patients were 49% and 18% lower respectively, than those of normal age-matched healthy controls, indicating that the complexity of various brain oscillations varies according to the level of consciousness (i.e., the unconscious brain-damaged patients showed a less complex EEG signal). These results corroborate our previous findings [32,38] in which the EEG BIS values of 13 VS/UWS and 30 MCS patients were 30% and 11% lower respectively than those of conscious brain-damaged controls. Similar results were also obtained in two recent studies using offline EEG entropy calculations in DOC patients. Sarà and Pistoia reported results for approximate entropy in 10 VS/UWS patients that were 33% lower than those recorded in 10 healthy controls [39]. Similarly, Wu and colleagues reported results for cross approximate entropy in 21 VS/UWS patients (studied <6 months) and in 16 MCS patients that were 27% and 8% lower respectively than those of 30 conscious but brain-damaged patients [40]. The latter study showed no difference at the group level between VS/UWS and MCS.

We here observed a reliable difference in entropy measurements between VS/UWS and MCS in the acute setting. A mean EEG entropy cut-off value of 52 in a 10-minute resting state epoch allowed us to distinguish between unconscious (coma, VS/UWS) and conscious (MCS) patients in the acute stage. The sensitivity and specificity of entropy recordings in distinguishing unconscious from minimally conscious patients were even better than the values previously reported using bispectral index measurements in VS/UWS and MCS patients studied within 11 weeks of the insult (sensitivity of 89% and specificity of 90% for EEG entropy versus sensitivity and specificity of 75% for BIS) [32]. Moreover, the bispectral monitor is a commercial tool that employs hidden mathematical algorithms not acceptable for scientific purposes. The EEG entropy measurement used in this study is therefore a surprisingly reliable (and easy-to-administer) tool that could assist clinical diagnosis in the early stage.

In chronic patients, VS/UWS patients showed no significant difference in entropy compared to MCS patients. This may reflect genuine time-dependent cortical reorganization and plasticity [41] or it could be related to (muscle) artifacts due to increasing spasticity over time. The importance of contamination by high-frequency muscle artifacts in the entropy calculation we employed is clearly illustrated in figure 3. Neuromuscular blocking (1mg/kg of intravenous rucuronium administered for clinical reasons independent of the present study 11 days after cardiac arrest) instantly reduced entropy measurements in one clinically comatose patient. This observation is in line with previous studies showing non-zero EEG entropy and BIS values due to muscle artifacts in patients with the clinical diagnosis of brain death [42,43].

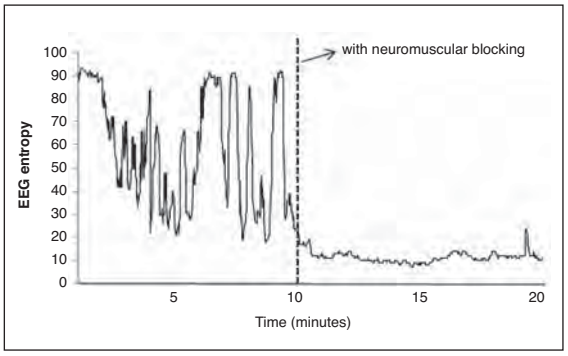


Figure 3 - Neuromuscular blocking reduces EEG entropy in a case of post-anoxic encephalopathy.

EEG entropy values were not found to differ according to etiology, suggesting that the technique can be used in both traumatic and in non-traumatic brain injured patients. In contrast to previous studies showing the prognostic value of the EEG BIS (at group level, [32]), we here failed to show any difference in initial entropy values between patients with good (i.e., recovery of functional communication) versus bad outcome at one-year follow up.

Finally, no difference was found between state entropy (designed to include only cortical EEG) and response entropy (also including frontal electromyogram) measurements. It should be stressed that the latter is developed merely to assess EEG reactivity to pain in general anesthesia settings [44] but seems less useful in the present context which assesses resting state EEG in DOC. Note that noxious stimulation did not significantly increase response entropy in a subgroup of 12 MCS, 12 VS/UWS and six comatose patients in the present cohort.

In conclusion, we here showed decreased complexity of neural networks, as measured by time-frequency balanced spectral entropy measurements in severely brain injured patients. User-independent EEG entropy measurements allowed us to distinguish unconscious (coma or VS/UWS) from minimally conscious patients in the acute stage with a sensitivity and a specificity superior to those previously reported for BIS measurements [38]. The automated entropy calculation paradigms employed should, however, be improved through future studies (e.g., multiresolution entropy [45] or Lempel-Ziv complexity [40]) in order to reduce artifacts such as those due to muscle spasticity. This could open the way for validating clinically user-independent EEG quantification in the specific context of disorders of consciousness. Other investigations should also be performed to verify the prognostic potential of the technique. Continuous online fronto-temporal EEG entropy monitoring, easily accessible at the bedside, may therefore constitute an additional method helping clinicians in the differential diagnosis of unsedated severely brain-injured patients recovering from coma. The current challenge is to document how these EEG and functional neuroimaging studies can improve our assessment and rehabilitation planning [46-48] in patients with disorders of consciousness.

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CHAPTER 6

Predictors of short-term outcome in brain-injured patients with disorders of consciousness ☆

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Abstract:
Objectives: To investigate predictors of recovery from the vegetative state (VS) and minimally conscious state (MCS) after brain injury as measured by the widely used Disability Rating Scale (DRS) and to explore differences in rate of recovery and predictors of recovery during inpatient rehabilitation in patients with non-traumatic (NTBI) and traumatic brain injury (TBI).

Design: Longitudinal observational cohort design and retrospective comparison study, in which an initial DRS score was collected at the time of study enrollment. Weekly DRS scores were recorded until discharge from the rehabilitation center for both NTBI and TBI patients.

Setting: Seven acute inpatient rehabilitation facilities in the United States and Europe with specialized programs for VS and MCS patients (the Consciousness Consortium).

Participants: One hundred sixty-nine patients with a non-traumatic (N = ~~50~~) and a traumatic (N = ~~41~~19) brain injury who were in the VS or MCS states.

Interventions: Not applicable.

Main Outcome Measures: DRS score at 13 weeks after injury; change in DRS score over 6 weeks post-admission; and time until commands were first followed (for patients who did not show command-following at or within 2 weeks of admission).

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Results: Both time between injury and enrollment and DRS score at enrollment were significant predictors of DRS score at week 13 post-injury but the main effect of etiology only approached significance. Etiology was however a significant predictor of the amount of recovery observed over the 6 weeks following enrollment. Time between injury and enrollment was also a good predictor of this outcome, but not DRS score at enrollment. For the time until commands were first followed, patients with better DRS scores at enrollment, and those with faster early rates of change recovered command following sooner than those with worse DRS scores or slower initial rates of change. The etiology was not a significant predictor for this last outcome. None of these predictive models explained sufficient variance to allow their use in individual clinical decision making.

Conclusions: Time post-injury and DRS score at enrollment are predictors of early recovery among patients with disorders of consciousness, depending on the outcome measure chosen. Etiology was also a significant predictor in some analyses, with traumatically injured patients recovering more than those with non-traumatic injuries. However, the hypothesized interaction between etiology and time post-injury did not reach significance in any of the analyses suggesting that, within the time frame studied, the decline in prognosis with the passage of time was similar in the two groups.

Keywords: brain injuries; minimally conscious state; vegetative state; Disability Rating Scale; following command; prognosis; consciousness

Introduction

Outcome prediction is a frequent topic in the literature on neurologic recovery and rehabilitation. However, one may have several different purposes in mind in outcome prediction and each of these purposes places different performance requirements on the predictive model. Relatively gross aggregate prediction of rates of recovery may suffice for the purpose of planning healthcare services, estimating costs, or generating payment schemes. Similar gross aggregate models may highlight predictor variables that may have theoretical interest as possible causal factors in recovery. A much more demanding use of outcome prediction is to assist in the healthcare decision making for individual patients. Here one might wish to avoid ''wasting'' resources on someone who will not show substantial recovery, and to ensure that someone with good recovery potential receives services that will optimize that recovery. In this context, even a relatively accurate aggregate model may make inaccurate predictions about substantial numbers of individual cases. Outcome prediction may also differ in the time frame of interest. In many cases, the ''final outcome'' is of greatest interest to predict, but when the model is being used to allocate clinical services, one may be interested primarily in the outcome within the time frame that those services will be provided.

Prediction of outcome among patients with disorders of consciousness (DOC) is still difficult to establish individually. Moreover, most prognostic studies have begun on the day of injury when the diagnoses of vegetative (VS) and minimally conscious states (MCS) are not yet defined, and have studied the full range of injury severity. This provides little guidance to clinicians who see patients who have evolved from coma into the VS or MCS, and who wish to assess the likelihood of further progress, to determine the appropriate level of treatment intensity, and to provide guidance to caregivers in their decision making.

It is known that among patients with DOC one month after injury, those who show some minimal signs of consciousness have a better chance of recovery than patients who are still in a VS at that time, and the earlier the return of consciousness is detected, the better is the outcome (Giacino and Zasler, 1997; Giacino and Whyte, 2005; Whyte et al., 2005; Giacino and Kalmar, 1997). The etiology is also a relevant predictor of recovery.

Traumatic brain injury (TBI) tends to have a better outcome than non-traumatic etiology (NTBI) (especially anoxia) (The Multi-Society Task Force on PVS, 1994b). Moreover, the recovery phase lasts longer for a traumatic etiology: it has been suggested that the term *permanent vegetative state* should not be applied until 1 year after traumatic injury whereas for a non-traumatic injury, this diagnosis may be applied after only 3 months (The Multi-Society Task Force on PVS, 1994a, b). Note that the term *permanent* implies zero probability of recovery and can therefore give rise to serious decisions about the cessation of medication and nutrition.

Potential recovery is also linked to the location, extent, and nature of the brain damage as well as to the condition of the brain before the injury. Young age of the patient and the absence of medical history (such as alcoholism, drug use, or mental illness) lead to a better outcome (The Multi-Society Task Force on PVS, 1994b; Laureys et al., 2001). For patients with DOC of traumatic origin, the Disability Rating Scale (DRS) at 16 weeks post-injury, and the time at which commands were first followed, during the acute rehabilitation hospitalization, were related to the DRS score at rehabilitation admission, the time between injury and admission, and rate of DRS change during the first 2 weeks of rehabilitation (Whyte et al., 2005). New assessment methods, such as event-related potential (ERP) techniques, and evaluation with functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scanning, offer promise in improving the precision of prognostic prediction, since they may help distinguish among patients with different neurophysiologic profiles (which confer different prognoses) at a time when behavioral assessments are at floor for all of them (Di et al., 2008; Owen et al., 2006; Schnakers et al., 2008; Kotchoubey, 2007). However, although these techniques appear to be able to identify a subgroup of VS patients with greater recovery potential or to identify subtle signs of consciousness not apparent on behavioral examination, they have not yet been used in systematic prediction at defined time points post-injury along with already known predictors.

Research on prediction of recovery from DOC is particularly challenging to conduct, at least in the United States, because intensive academically oriented healthcare services are severely restricted for this patient population after the first few weeks post-onset. This is based on a general pessimism that meaningful recovery is unlikely, the belief that the process of rehabilitation requires a level of voluntary participation that such patients cannot meet, and the sense that there is little evidence that intensive rehabilitation services can alter the outcome. Thus, such patients are generally dispersed to family homes or non-specialized nursing care facilities soon after injury, and, accordingly, lost to involvement in longitudinal research.

Because many of the available outcome studies follow a sample from the time of injury, so that a large proportion of the sample (those with milder injury) regain consciousness quickly, predictors of outcome in this rapidly recovering population may not apply to the sample with prolonged DOC. Other studies have followed patients with DOC for longer intervals, but typically restrict their prediction to the return of consciousness as a dichotomous variable (e.g., Multi-Society Task Force), shedding little light on the overall level of functional recovery. In this context, therefore, it is important to examine whether those patients with DOC who are available for study show sufficient recovery during the subacute period to suggest greater rehabilitation potential than is currently appreciated. In addition, if predictors of their short-term outcome are sufficiently accurate to guide individual service decisions, then these could be used to help tune rehabilitation admission criteria to accept the individuals with the greatest potential to benefit, and to avoid admitting individuals who will fail to make progress, and may present difficult placement problems. In this context, then, a number of important outcome questions need to be addressed. (1) As a group, how much recovery do patients admitted with DOC make in the subacute period? (2) Are there variables, available at the time that admission decisions are being made, that can help predict the amount of functional recovery that will occur in the time span over which rehabilitation services

might be delivered? (3) Are there differences in the factors that predict recovery for patients with traumatic versus non-traumatic injuries during this interval?

We hypothesized that substantial recovery would be seen in a large proportion of patients who present with DOC in the first few weeks after brain injury. We also hypothesized, based on prior studies and our own previous work with a pure sample of individuals with traumatic brain injuries, that the etiology of injury (in particular traumatic vs. non-traumatic), the time post-event at which the patient was admitted to rehabilitation, and the functional level at which they were admitted, would all predict differences in the short-term recovery seen over the ensuing weeks.

Methods

Participants in this research were enrolled from the Consciousness Consortium (CC), which consists of a set of facilities in the United States and Europe that have specialized programs for the care and rehabilitation of patients with DOC, and an interest in conducting research in this area. The CC began a longitudinal descriptive study in 1996, and reported the results of the traumatic sample ($n = 424$) in 2005 (Whyte et al., 2005) which laid the groundwork for a randomized controlled treatment study currently underway (Giacino and Whyte, 2003; Whyte, 2007). Here we report the data for the non-traumatic sample also enrolled by CC facilities, and also analyze comparative results for the two subsamples.

Participants

Participants were enrolled in the study between December 1996 and June 2001 when they were admitted to one of the seven CC-member rehabilitation centers. Admission criteria were a severe acquired brain injury of traumatic or non-traumatic etiology and a DRS score on admission greater than 15, with no more than inconsistent command-following. These score criteria were chosen because all patients in VS or MCS should have DRS scores of at least 16, but lack of consistent command following helps ensure that those who have emerged from MCS are excluded. One hundred forty-eight (148) traumatic and 77 non-traumatic patients diagnosed as vegetative or minimally conscious on admission were entered into the longitudinal database. However, because specific variables required for the analyses were missing from some participants, the number of participants included in this report is smaller (see Table 1 for details).

Note that there is a bias of selective admission in rehabilitation centers. Indeed, acute inpatient rehabilitation facilities tend to select, to varying degrees, candidates who are believed to have a

Table 1. Outcome variables

	Traumatic brain injury (TBI)			Non-traumatic brain injury (NTBI)			Definition
	No. of subjects	Mean/median/SD	Min./max.	No. of subjects	Mean/median/SD	Min./max.	
DRS_{13}	99	18.14/20/5.65	5/28	36	19.72/20.5/4.3	9/26	DRS score at week 13 post-injury
$Change_{DRS6}$	99	4.96/4/4.23	−2/11	36	2.86/2.5/2.93	−1/16	[DRS score at enrollment]–[DRS score 6 weeks later]
T_{Follow}	71	62.04/30/79.72	0/473	37	42.27/27/44.73	0/196	[Date of command following or date of discharge if not following commands]−[date of 2 weeks post-admission]

chance of recovery and who will benefit from intensive therapy. Admission is therefore based, at least informally, on various prognostic factors that are perceived to be positive indicators of functional improvement (e.g., recent injury, possible signs of consciousness, etc.). Thus, this is not a population-based study, although it is relevant to decision making in the types of facilities in which the study was conducted.

The study was determined by the relevant Institutional Review Boards to be exempt from the need for individual informed consent because it involved only anonymous recording of observational data but no changes in clinical care.

The Disability Rating Scale (DRS)

The DRS is a measure of impairment, disability (now referred to as ''activity''), and handicap (now referred to as ''participation'') across the span of recovery to track an individual from coma to community (Rappaport et al., 1982). The first three items of the DRS (''Eye Opening,'' ''Communication Ability,'' and ''Motor Response'') reflect impairment ratings whereas cognitive ability for ''Feeding,'' ''Toileting,'' and ''Grooming'' reflect the level of disability and, finally, the ''Level of Functioning'' item reflects handicap, as does the last item, ''Employability''. The DRS is scored from 0 (no disability) to 29 (extreme VS). Note that this scale does not disentangle VS from MCS because it was constructed before the development of the MCS criteria (Giacino et al., 2002).

Data collection

For those patients who met the enrollment criteria for this study, demographic information, injury history and early complications, and admission DRS score were recorded. DRS scoring was repeated weekly as long as the patient remained at the facility. Data were recorded on paper forms and then faxed or mailed to the data center at the Moss Rehabilitation Research Institute, where they were entered into a computer database. For these analyses, the database was queried for demographic information (age, gender, ethnicity), the cause of injury (traumatic or non-traumatic brain injury), the time between the injury and the admission to the rehabilitation facility, the DRS score on admission, the weekly DRS score until discharge, and the time between the admission and the first command following (if not present at admission).

Three outcomes were addressed in the analyses: the DRS score at 13 weeks after injury (DRS_{13}), the change in DRS score over 6 weeks post-admission ($Change_{DRS6}$), and the time until commands were first followed for patients who did not show command following at or within 2 weeks of admission (T_{Follow}). Patients that did not follow commands during admission were censored at the discharge time. The operational definition of each outcome is reported in Table 1. DRS score at 13 weeks post-injury was chosen because the largest sample was available at that time and DRS score over 6 weeks post-enrollment was selected because it is the average length of stay in the rehabilitation facilities. For practical relevance, T_{Follow} would ideally be calculated from the time of admission since a clinician admitting a patient wants to know whether and when he/she will begin to follow commands thereafter. Moreover, calculating this index from the time of injury would be problematic in this sample, since many injured individuals would have recovered command following much earlier, but would not be included in the sample. However, because the rate of functional improvement in the first 2 weeks after admission was used as one of the predictor variables (see below for details), in fact we attempted to predict recovery of command following from that point forward.

Of the participants meeting the enrollment criteria, only those who had complete data for the outcome and predictor variables were used in each analysis (see Tables 1 and 2). This resulted in an effective sample of 135 (99TBI, 36NTBI) for the DRS_{13} and $Change_{DRS6}$ analyses and 108 (71TBI, 37NTBI) for the T_{Follow} analysis. Out of these 108 patients, 48 were censored at the time of discharge. Seventy-four (74) participants (50TBI, 24NTBI) were included in all of the analyses.

Table 2. Predictor variables

	DRS_{13} and 6-week change		T_{Follow}	
	TBI ($N = 99$)	NTBI ($N = 36$)	TBI ($N = 71$)	NTBI ($N = 37$)
Continuous variables	Mean/median/SD	Mean/median/SD	Mean/median/SD	Mean/median/SD
Age	31.58/28/14.09	40.78/39.5/16.33	28.79/26/12.54	36.89/35/14.85
$\text{Log}T_{enroll}$	5.55/5.39/0.55	5.44/5.51/0.49	5.59/5.39/0.59	6.05/5.73/1.29
(T_{enroll})	(50.4/42/20.15)	(45.75/45.5/14.18)	(52.37/42/23.07)	(115.49/53/186.19)
DRS_{enroll}	22.85/23/2.23	23.06/23/2.57	23.84/24/2.14	23.84/24/1.72
Nominal variables	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)
Gender				
Male	67 (67)	15 (41.7)	54 (76.06)	13 (64.86)
Female	32 (32.3)	21 (58.3)	17 (23.94)	24 (35.14)
Ethnicity				
White	77 (77.8)	29 (80.5)	61 (85.91)	28 (75.68)
Non-white	22 (22.2)	7 (19.4)	10 (14.09)	9 (24.32)

Abbreviations: $\text{Log}T_{enroll}$: $\log_2$ transformation of T_{enroll}; T_{enroll}: date of command following−date of enrollment; DRS_{enroll}: DRS score at enrollment.

The characteristics of the patients in both analyses sets are shown in Table 2.

Data analysis

The independent variable *time to enrollment* (T_{enroll}) was log transformed ($\text{Log}T_{enroll}$), since the assumption of linear association with the outcome was more appropriate on the log scale. NTBI and TBI were analyzed jointly to allow evaluation of the difference in outcomes by etiology. Different statistical models were used for the different outcomes. DRS at week 13 and the change in DRS scores 6 weeks post-admission were analyzed on a total of 135 observations using the robust MM regression (Yohai, 1987), since distributions of residuals from the standard multiple regression models exhibited heavy tails compromising the normality assumption. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors of DRS at week 13 and change in DRS scores 6 weeks post-admission. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the models. The final models included the etiology, admission DRS, and time to enroll and controlled for potentially important age difference. Other demographic variables, which were not significantly associated with outcome, were excluded from the models.

For the last outcome, the time until commands were first followed, the analyses were performed on a partially overlapping sample because some patients in the previous analyses had already followed commands before admission and because some patients were admitted after 13 weeks post-injury. A Cox proportional hazards model was initially fitted to the time from admission to follow commands. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the model. Data from 169 patients were available for these analyses. Because the proportional hazards assumptions were not satisfied, the 2-week rate of change in DRS was also introduced into Cox model, which improved the overall model fit. In the earlier work (Whyte et al., 2005), the 2-week rate of change in DRS was found to be a strong predictor of the time to follow commands in TBI patients. Time from 2 weeks post-admission until commands were followed was then modeled. The final Cox model was based on 108 patients who also had 2-week rate of change in DRS available and did not follow commands within the first 2

weeks of admission. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the model.

Results

DRS score at week 13

None of the demographic variables was significantly associated with DRS score at week 13, but age was retained in the model because of prior research suggesting that age may influence the pace of neurologic recovery (Millis et al., 2001; Ritchie et al., 2000). Both time between injury and enrollment ($\text{Log}T_{\text{enroll}}$) and DRS score at enrollment ($\text{DRS}_{\text{enroll}}$) were highly significant predictors of DRS score at week 13 post-injury. The main effect of etiology approached significance (difference = 1.4, 95% CI: −0.2, 3.0; $p = 0.083$). However, the interactions between etiology and DRS at enrollment and time to enrollment were not significant. Table 3 reports the slopes for the different predictors from the final model. The model implies that an increase of 1 point in DRS at enrollment translates on average into a 1.2 point increase in DRS at week 13 (note that higher DRS scores indicate worse outcomes). Meanwhile doubling of the time to enrollment (1 unit increase of the $\text{Log}T_{\text{enroll}}$) implies a 3.7 point increase in DRS at week 13. Thus, this analysis did not provide strong evidence for a difference in the recovery pattern between TBI and NTBI patients during this time frame. Finally, the R^2 is 0.355 for this robust regression model.

DRS score improvement over the 6 weeks post-enrollment

Etiology was a significant predictor of the amount of recovery observed over the 6 weeks following enrollment. On average TBI patients had 2.0 points (95% CI: 0.4, 3.5; $p = 0.011$) greater improvement in DRS scores over the 6-week interval than NTBI patients. In this analysis, time until enrollment, but not DRS score at enrollment was a significant predictor of recovery. Table 4 reports the slopes for the different predictors in the final model. The model implies that doubling of the time to enrollment (1 unit increase of the log base 2 transformed time to enroll) implies ~1.9 point reduction in the DRS change over this interval. Once again, the interaction between etiology and $\text{DRS}_{\text{enroll}}$ and $\text{Log}T_{\text{enroll}}$ was not significant. Thus, although NTBI patients showed less recovery, during this interval, this lesser degree of recovery was not accounted for by a more prominent decline in prognosis with the passage of time. Note that the R^2 for this robust regression model is only 0.094.

Time to follow commands

The final model was reduced to two significant predictors plus etiology, because models incorporating additional non-significant covariates did not yield adequate goodness-of-fit test results. As noted in Table 5, with inclusion of the 2-week rate variable, etiology was not a significant predictor of the time until commands were followed.

Table 3. Results for the robust regression model for DRS at week 13

	Slope or difference[a]	95% confidence limits		*p*-value
		Lower	Upper	
Etiology[a]	1.4	−0.2	3.0	0.083
$\text{Log}T_{\text{enroll}}$	5.4	3.6	7.2	<0.0001
$\text{DRS}_{\text{enroll}}$	1.12	0.9	1.5	<0.0001
Age	0.0	−0.1	0.0	0.565

[a]Difference between TBI and NTBI groups.

Table 4. Results from the robust regression model for the change in DRS scores 6 weeks post-admission

	Slope or difference[a]	95% confidence limits		*p*-value
		Lower	Upper	
Etiology[a]	2	0.4	3.5	0.011
$\text{Log}T_{\text{enroll}}$	−1.87	−3.12	−0.62	<0.003
$\text{DRS}_{\text{enroll}}$	−0.14	−0.42	0.15	0.358
Age	0.03	−0.01	0.08	0.184

[a]Difference between TBI and NTBI groups.

Table 5. Results from the Cox model for time to follow commands from 2-week admission

	Hazard ratio	95% hazard ratio confidence limits		*p*-value
		Lower	Upper	
Etiology	1.14	0.66	1.98	0.637
$\text{DRS}_{\text{enroll}}$	0.87	0.77	0.99	0.033
2-week rate	11.26	1.65	76.67	0.013

However, both $\text{DRS}_{\text{enroll}}$ and the 2-week rate of change were significant predictors. Patients with lower (better) DRS scores at enrollment, and those with faster early rates of change recovered command following sooner than those with higher DRS scores or slower initial rates of change.

Discussion

These results demonstrate that considerable recovery is possible during the typical time frame of acute rehabilitation care, for both TBI and NTBI patients. Overall 83.7% of patients improved their DRS score by at least 1 point over the 6 weeks of observation (84.8% of TBI and 80.5% of NTBI), and 61.1% of those who were not following commands at admission began to follow them prior to discharge (67.6% TBI and 48.6% NTBI). How much rehabilitation services enhance this recovery is unknown, but these findings suggest that the majority of patients who are admitted to acute rehabilitation will demonstrate meaningful recovery.

These results also confirm, in a sample of TBI and NTBI patients followed in a comparable manner, that time between injury and enrollment is a key predictor of recovery, with the passage of time reducing the chances of recovery. This was true for DRS_{13} and for 6-week change, but not for the time until commands were followed. However, in the latter analysis, direct measurement of the rate of recovery, captured by the 2-week change variable, may have reduced the significance of the more indirectly predictive T_{enroll} variable. The DRS score at enrollment was predictive of the DRS score at 13 weeks post-injury, but not of the amount of recovery that would be seen over a defined interval, suggesting that the admission DRS score is primarily a predictor of functional *status* rather than functional *change*, whereas the time until enrollment is particularly relevant to the probability of *change*. DRS at enrollment was also predictive of the time at which commands would be followed. This may indicate that, at equivalent rates of change, patients who start at a better functional level need less improvement (and hence less time) to reach the criterion of command following.

The effects of etiology on outcome in this study were more complex. NTBI patients had significantly or marginally worse outcomes in terms of 6-week change and DRS_{13}, respectively, but etiology was not a significant predictor of time until commands were followed. As mentioned above, the inclusion of the 2-week rate of change

in the latter model, necessitated for statistical reasons, may have reduced the significance of less direct predictors such as time post-injury or etiology. Even though NTBI patients had somewhat poorer outcomes than TBI patients, depending on the outcome measure chosen, the specific prediction that the prognosis of NTBI patients would decline more precipitously over time (i.e., an interaction between etiology and $\mathrm{Log}T_{\mathrm{enroll}}$) was not supported. This is in contrast to prior studies suggesting that the ''window of recovery'' is shorter for NTBI than for TBI patients (The Multi-Society Task Force on PVS, 1994b). However, the differential impact of time may be more dramatic in the 3–12 month range, whereas these data were collected primarily in the early weeks post-injury.

In the aggregate, these results confirm the importance of etiology, initial functional status, and time since injury in determining outcome in individuals with DOC. However, the majority of the variance in individual outcome remains unaccounted for. The final models described here account for approximately 35.5% of the variance in DRS_{13}, and about 9% of the variance in 6-week change. Thus, these predictors cannot be used with confidence to predict the outcomes of individual patients or to make admission decisions, without a high risk of error in both directions.

This study has a number of important limitations. Most importantly, it was conducted on a select referral sample, not a population-based sample. Thus, the large proportion of patients who recover in hours or days after injury are not included in the analysis. But even if one focuses on those patients who might be considered for rehabilitation care because they are still suffering from DOC several weeks post-injury, this remains a biased sample, since it involved only those patients who were admitted to rehabilitation services but not those who were not referred or were referred but not admitted. The specific clinical factors used in making those admission decisions are unknown, but surely may have included some subtle prognostic factors. In particular, since clinicians are generally aware of the more negative prognosis of NTBI patients reported in the literature, they may have had more stringent admission screening of non-traumatic referrals than of traumatic referrals. This, in turn, may have led to smaller differences in outcome based on etiology than might be seen in a less selected sample. This implicitly assumes, however, that some of the variance in recovery not accounted for by the predictors used in this study, was accounted for by unmeasured variables available to clinical decision makers, rather than simply being altogether unexplained. There is no direct evidence for a more stringent admission screening of NTBI patients since, for example, their DRS scores at enrollment were actually slightly worse than those of the TBI patients. Finally, the relatively short-term nature of this study, constrained by the current realities of acute inpatient rehabilitation stays in the United States, meant that a substantial number of patients were not following commands by the time of discharge and were censored in the Cox analysis. Longer intervals of follow up and larger samples, particularly of those with non-traumatic injuries might have more clearly informed the pattern of recovery.

Conclusion

In this selected sample of patients with DOC, referred and approved for inpatient rehabilitation admission, significant recovery was seen over the hospital stay, with the majority of patients with both traumatic and non-traumatic injuries demonstrating improvements in DRS scores and, among vegetative patients, the development of command following. The time between injury and rehabilitation admission and the DRS score at admission were each predictive of two of the three outcomes. Etiology was predictive of amount of functional improvement seen over 6 weeks of hospitalization, but less so of the DRS score at 13 weeks post-injury or the time until commands were followed. In the one model in which early rate of change was included, it was strongly predictive of outcome while etiology was not, suggesting that the clinical trajectory, itself, is highly predictive. None of the predictive outcome models accounted for sufficient variance to be used in individual clinical decision making.

Abbreviations

CC	Consciousness Consortium
$\text{Change}_{\text{DRS6}}$	change in DRS score over 6 weeks post-admission
DOC	disorders of consciousness
DRS	Disability Rating Scale
DRS_{13}	Disability Rating Scale score at 13 weeks after injury
$\text{DRS}_{\text{enroll}}$	Disability Rating Scale score at enrollment
ERP	event-related potential
fMRI	functional magnetic resonance imaging
$\text{Log}T_{\text{enroll}}$	log transformation of the time between injury and enrollment
MCS	minimally conscious state
NTBI	non-traumatic brain injury
PET	positron emission tomography
PVS	persistent vegetative state
TBI	traumatic brain injury
T_{enroll}	time between injury and enrollment
T_{Follow}	time until commands were first followed for patients who did not show command following at or within 2 weeks of admission
VS	vegetative state

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Transcranial Magnetic Stimulation in Disorders of Consciousness

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ABSTRACT

We have reviewed the literature on transcranial magnetic stimulation studies in patients with brain death, coma, vegetative, minimally conscious, and locked-in states. Transcranial magnetic stimulation permits non-invasive study of brain excitability and may extend our understanding of the underlying mechanisms of these disorders. However, use of this technique in severe brain damage remains methodologically ill-defined and must be further validated prior to clinical application in these challenging patients.

KEY WORDS

coma, vegetative state, minimally conscious state, consciousness, brain injury, transcranial magnetic stimulation

INTRODUCTION

Severe brain injuries constitute a growing public health problem. Improvements in intensive care have led to an increasing number of patients surviving acute brain injury. Currently, however, patients who suffer traumatic, anoxic or other severe brain injuries are viewed as a homogeneous group with hopeless outcome /73/. In clinical practice, the diagnosis of outcome in chronic disorders of consciousness comes from bedside clinical and behavioural assessment. For disorders of consciousness like vegetative state (VS), motor dysfunction and arousal fluctuations render the bedside assessment of awareness challenging /62/. Misdiagnosis in VS has been shown to be as high as 37-43% /4,87/. The clinical assessment of motor function in this patient population is an important parameter and is therefore included in the Glasgow Coma Scale (GCS) and other coma scales. Furthermore, in ventilated comatose patients the GCS mainly reflects the best motor response, as the score for ocular and verbal responses is often equal to one. If the motor function is an essential parameter in the evaluation of the level of consciousness, objective neurophysiological investigation must be included in the assessment of the depth of coma and chronic disorders of consciousness.

This review first provides a brief introduction of the technique of transcranial magnetic stimulation (TMS), and then discusses the present status of studies performed in disorders of consciousness. We have included here papers on TMS in brain death, coma, VS, minimally conscious (MCS), and locked-in states (LIS). Articles published in English were included using Medline and ISI Web of Knowledge databases; the search was performed in September 2008; search terms were "transcranial magnetic stimulation" or "magnetic stimulation" AND "brain injuries" or "coma", "coma, post-head injury", "brain death", "persistent vegetative state", "consciousness disorders", "unconsciousness", "quadriplegia", "locked in syndrome". In addition, references in the articles were inspected to identify

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additional studies. Although most of the studies investigated combination of TMS with other electrophysiological and neuroimaging techniques, in the present review we mainly focus on the TMS results.

We discuss in this review how TMS may contribute to our understanding of the pathophysiology of disorders of consciousness. Finally, we also suggest perspectives for applying TMS in these challenging patients.

GENERAL PRINCIPLES OF TMS

The first experiments of stimulation the motor cortex through the intact scalp used brief high-voltage electrical shocks (transcranial electrical stimulation) /67/, but stimulation at the relevant intensities usually generated strong scalp pain. The development of TMS /7/ overcame this problem of undesirable discomfort by using a magnetic field to carry the electrical stimulus through the scalp and skull to the brain. By placing a wire on the scalp and passing a powerful and rapidly changing current through it, a magnetic field is produced that penetrates the cranium and induces an electrical current in the area of the brain lying beneath the coil, which in turn penetrates the membranes of the neurons, resulting in excitatory or inhibitory post-synaptic potential (reviewed in /25/). In classical TMS experiments, stimulation is delivered to the primary motor cortex, and motor evoked potentials (MEPs) are recorded from a muscle using surface electromyography electrodes. TMS may activate, inhibit or interfere with the activity of various cortico-cortical and cortico-subcortical networks according to the parameters of stimulation (stimulation site and coil orientation, biphasic and monophasic stimulation, stimulus intensity and frequency), and the effects of TMS occur during the time of stimulation or may induce more prolonged changes. Factors contributing to variability of MEPs include muscle activation or resting state of the target muscle /38,60/, non-specific facilitation, such as facial muscle contraction and eye movements during recordings from hand muscles /2/, and the subject's mental activity during testing /31,39,74,81,96/. Certain neurological disease states influence the TMS measures (for review see /15/) although spasticity and hyperreflexia do not facilitate MEP responses to TMS /13/. TMS is though to activate the corticospinal neurons transsynaptically /24/, and is more susceptible than transcranial electrical stimulation to inhibitory drug effects, but on the other hand, could have a have higher sensitivity to detect superficial, presynaptic lesions. The effects of different drugs on TMS measures are reviewed by Ziemann /104/ (see Table 1).

It is well accepted that TMS is capable of activating intracortical inhibitory neurons within the motor cortex by using a paired-pulse TMS paradigm /53/. Here a magnetic subthreshold conditioning stimulus causes suppression of the response in the muscle to a suprathreshold test shock if given 1-6 msec earlier (i.e. intracortical inhibition; ICI). In contrast, if the two stimuli are separated by 10 to 15 msec, the response to the test stimulus is facilitated (i.e. intracortical facilitation; ICF). ICI is not observed when the test stimulus is evoked electrically instead of magnetically, which suggests an inhibitory phenomenon taking place at the cortical level /28/. It is also suggested that the inhibitory effect is the result of the firing of GABA (γ-aminobutyric acid)-ergic interneurons within the motor cortex /10,107/.

Functional connectivity between different cortical regions can be investigated by TMS. Transcallosal connections between the two cerebral hemispheres were first studied by Ferbert *et al.* /33/ by applying a conditioning stimulus to one hemisphere while applying a test stimulus to the other. Transcallosal output gives rise to inhibition of the contralateral primary motor cortex /40,68,98/. The ipsilateral silent period (i.e. when TMS is delivered over the motor cortex during voluntary muscle contraction, a pause in ongoing electromyography activity follows the evoked MEPs) is also ascribed to transcallosal inhibition and is suggested as a possible marker for the severity of traumatic brain injury /93/. Transcallosal inhibition has been shown to be absent in some patients with corpus callosum lesions as they are believed to involve transcallosal pathways /69/. Afferent input is also shown to modify the excitability of the motor cortex with a complex time course /61,95/. This inhibitory

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phenomenon is termed short latency afferent inhibition and is thought to be regulated by muscarinic cholinergic circuits /29/. Fujiki *et al.* /37/ have found that the amount of short latency afferent inhibition was significantly smaller in patients with diffuse axonal injury and was also significantly increased by a single dose of the acetylcholinesterase inhibitor donepezil.

Single and paired pulses guarantee a high temporal precision (in the ms range). If a train of multiple pulses is applied at a particular frequency, the stimulation is called repetitive TMS. In contrast to single pulse TMS (spTMS), multiple pulses have more prolonged effects on the brain. The nature of the after-effects depends on the number, intensity and frequency of stimulation pulses. For example, stimulation at frequencies lower than 1 Hz reduces cortex excitability /14,79/ while stimulation at frequencies higher than 1 Hz tends to increase rather than decrease cortical excitability /9/. Changes in excitability of the neuraxis observed during repetitive TMS appear complex (reviewed in /35/) and require both studies in humans and in animal models to explore the underlying mechanisms. Because repetitive TMS of the cortex has the potential to induce epileptic activity, safety limits have been published for use of repetitive TMS in humans (reviewed in /97,99/).

Despite wide use of the TMS techniques in neuroscience, only 11 studies on TMS in acute and chronic disorders of consciousness have been published in the past 20 years (Table 2).

TMS IN BRAIN DEATH

Two studies have been published on electrophysiological examination of motor function in brain death. Firsching *et al.* /34/ used spTMS to obtain MEPs in 51 comatose patients with primary brain lesions within 48 hours of the onset of coma and followed them progressively up to the onset of brain death. Absence of MEPs prior to the apnoea test was observed in 15 patients, after the apnoea test absence was documented in 36 patients. The stepwise abolition of initially intact MEPs with the onset of brain death was observed in 12 patients, and at the time of absence of the cranial nerve reflexes MEPs were abolished in all patients. SpTMS was also used by Ying *et al.* /101/ in three brain-dead patients, and in all patients MEPs were reported absent.

These studies show that TMS can document the absence of motor cortex function in brain death, but TMS has only a limited role in the assessment of brain death as other diagnostic criteria of brain death are well defined /1,54/.

TMS IN COMA

Five studies evaluated cortical MEPs in the acute phase of coma and correlated the findings to clinical outcome. In the study already mentioned above, Ying *et al.* /101/ also examined 23 comatose patients. SpTMS could not elicit MEPs in 13 patients in basal conditions, but if administrated together with a painful twisting stimulus to the skin of the upper arm, spTMS elicited clearly discernible MEPs in five of these patients. The authors found that MEPs were bilaterally absent in five out of 15 patients with poor outcome (either death or VS), and in four patients with poor outcome MEPs could only be elicited during painful stimulation. On the other hand, MEPs were present bilaterally in basal conditions in six patients with poor outcome. Painful stimulation has also been applied just before each magnetic stimulus to facilitate MEP responses in a study of 22 comatose patients recorded within one week after onset of the coma /32/. Out of 22 traces (recorded from 11 patients) 12 were absent in the "relaxed" condition, while only one was absent in the "contracted" condition. Nine out of ten patients with bilaterally absent MEPs were either dead or in VS at the end of the follow-up. However, one out of ten patients with bilaterally absent MEPs showed a good recovery. Unfortunately this patient was not submitted to serial recordings to evaluate the reappearance of the MEPs. Zenter and Rohde /103/ used transcranial electrical stimulation to evaluate MEPs in a total of 213 comatose patients, and additionally performed spTMS in 39 cases. Examination was done within one to three days after insult, and evoked potentials were correlated with the outcome of the patients, assessed by the Glasgow Outcome

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TABLE 1

Pharmacological modulation of TMS measures of motor cortex excitability

Reference	Drug	Mode of action	MT	MEP	CSP	SICI	ICF	SAI
Anticonvulsants								
Ziemann *et al.* /107/ SchulzeBonhage *et al* /88/	Carbamazepine	Na^+ blockade of voltage-gated sodium channels	↑–	÷	÷	÷	↓÷	
Chen *et al.* /16/ Movroudakis *et al.* / 64/	Phenytoin	Na^+ blockade of voltage-gated sodium channels	↑↑	––	–÷			
Ziemann *et al.* /107/ Boroojerdi *et al.* /10/ Tergau *et al.* /94/	Lamotrigin	Na^+ blockade of voltage-gated sodium channels	↑↑↑	↓	÷–	–÷	–÷	
Ziemann *et al* /107/ Movroudakis *et al.* /65/	Vigabatrin	agonist at the $GABA_A$ receptor	–	–	–	÷	↓	
Werhahn *et al.* /100/	Tiagabine	agonist at the $GABA_A$ receptor	÷	–	↑	↓	↑	
Benzodiazepines								
Ziemann *et al.* /106/ Di Lazzaro *et al.* /23/ Boroojerdi *et al.* /10/	Lorazepam	agonist at the $GABA_A$ receptor	–––	↓↓	↑	↑↑–	↓–	↓
Inghilleri *et al.* /50/ Palmieri *et al.* /76/ Ilic *et al.* /49/	Diazepam	agonist at the $GABA_A$ receptor	––	↓–	↓÷	↑÷	↓	
Barbiturates								
Inghilleri *et al.* /50/	Thiopental	agonist at the $GABA_A$ receptor	–	↓	÷			
Antispasticity drugs								
Ziemann *et al.* /107/ Inghilleri *et al.* /50/	Baclofen	agonist at the GABAB receptor	–÷	÷÷	÷÷	↑	↓	
Kim *et al.* /51/	Botulinum toxin type A	ACh inhibitor at the neuromuscular junction	–	–	↑	↑	↓	

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Reference	Drug	Mode of action	MT	MEP	CSP	SICI	ICF	SAI
Analgesic drugs								
Di Lazzaro *et al.* /27/	Ketamine	NMDA antagonist	↓	↑	÷	÷	–	
Antiparkinson drugs								
Priori *et al.* /78/ Ziemann *et al.* /108/	L-DOPA	DA precursor	÷	÷	↑	÷	–	
Ziemann *et al.* /105/	Pergolide	DA agonist	÷	÷	↑	↑	–	
Atypical antipsychotics								
Ziemann *et al.* /108/ Daskalakis *et al.* /21/	Haloperidol	DA antagonist	÷÷	↑	–	↓÷	↑	
CNS stimulans drugs								
Ilic *et al.* /48/ Moll *et al.* /70/	Methylphenidate	NE agonist	––	↑	–	↓÷	↑÷	
Boroojerdi *et al.* /10/	d-Amphetamine	NE/DA agonist	÷	↑		÷	↑	
Antidepressants								
Ilic *et al.* /47/	Sertraline	serotonin re-uptake inhibitor	÷	↑	÷	–	↓	
Eichhammer *et al.* /30/	Citalopram	serotonin re-uptake inhibitor	÷			↑	÷	
Anticholinergic drugs								
Liepert *et al.* /58/	Atropine	M_1/M_2 muscarinic receptor antagonist	–	–	÷	↓	↑	
Di Lazzaro *et al.* /26/	Scopolamine	M_1 muscarinic receptor antagonist	↓	↑	÷	÷	÷	↓
Acetylcholinesterase inhibitors								
Di Lazzaro *et al.* /29/	Rivastigmine	Ach esterase inhibitor						↑

÷ = no effect; ↓ = reduction; ↑ = increase; combination ↑÷ or ↓÷ = controversial results in different studies; MT = motor threshold; MEP = motor evoked potential; CSP = cortical silent period; SICI = short intracortical inhibition; ICF = intracortical facilitation; SAI = short latency afferent inhibition; GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; Ach = acetylcholine; DA = dopamine; NE = norepinephrine.

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TABLE 2

TMS studies in disorders of consciousness

Reference	Aetiology*[1]	Level of consciousness*[2]	TMS interval*[3]	Drugs used	TMS paradigm	Main results
TMS in brain death						
Firsching *et al.* /34/	T (n=23) NT (n =28)	Brain death	TMS within 2 days	No barbiturates; no sedatives	1) SpTMS motor area (upper limbs); 2) Onset latency and MEPs amplitude	1) No MEPs at the first recording (n=39); 2) Stepwise abolition of initially intact MEPs with the onset of brain death (n=12); 3) No MEPs in patients with cranial nerve areflexia
Ying *et al.* /102/	NA	Brain death (n=3)	TMS within 1-35 days	No muscle relaxants; no sedation for 12 hours	1) SpTMS motor area (upper limbs); 2) Onset latency and MEPs amplitude	Absent MEPs bilaterally
TMS in coma						
Ying *et al.* /101/	T (n=11) NT=12	GCS 3-8 (n=19) GCS 9-11 (n=4)	TMS: 1-50 days after onset of coma; Clinical outcome 1-90 days (death); 6-20 months (survivors)	No muscle relaxants; no sedation for 12 hours	1) SpTMS motor area (upper limbs); 2) Onset latency and MEPs amplitude	1) TMS performed in the patients at rest insufficient to elicit MEPs (n=13) 2) TMS administrated together with a painful twisting stimulus elicit MEPs (n=5)
Facco *et al* /32/	T (n=13) NT(n=9)	GCS range 4-8; Motor function: extension (n=6), abnormal flexion in upper limbs (n=8), normal flexion and localization of the painful stimuli (n=8)	TMS within 7 days Clinical follow-up: time is NA	Phenobarbital 100 mg x 2 daily (n=22)	1) Sp TMS motor area (upper limb); 2) Onset latency and MEPs amplitude; 3) Facilitation of the response with painful stimulus, TMS giving during motor response	1) 12 out of 22 traces (recorded from 11 patients) were absent in the "relaxed" condition 2) Only one out of 22 was absent in the "contracted" condition 3) Nine out of 10 with bilaterally absent MEPs: death or VS 4) One out of ten patients with bilaterally absent MEPs: good recovery

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Reference	Aetiology*[1]	Level of consciousness*[2]	TMS interval*[3]	Drugs used	TMS paradigm	Main results
Zentner *et al.* /103/	n=39, aetiology NA	GCS less than 8	TMS within 1-3 days after onset Follow-up (GOS) 3 months and 2 years	NA	1) SpTMS motor area (upper limbs); 2) Onset latency and MEPs amplitude	1) Bilaterally absent MEPs 13 out of 18 patients: death or VS, none showed good recovery 2) Normal MEPs: two out of seven showed good recovery
Mazzini *et al.* /66/	T (n=27)	GCS range 6-10 Coma duration no less than 10 days	TMS :10-90 days Follow-up (TMS + GOS): 6 and 12 months after trauma	NA	1) SpTMS motor area (upper and lower limbs); 2) Onset latency and MEPs amplitude; 3) Sensitive input applied to the skin: stimulation induced grasp (hand) and plantar flexion (leg)	1) All measures (except of MEPs from lower limbs) showed a high negative predictive value
Schwarz *et al.* /89/	T (n=2) NT (n=28)*[4]	Onset: GCS <7 (n=6) GCS = 7-12 (n=10) GCS>12 (n=14) TMS examination: fully awake n=1; somnolent n=7, stuporous n=12; comatose n=10 (standard score NA)	MEP: immediately after emergency treatment (exact time NA); Clinical outcome (motor deficit and GOS): three months later	No sedation for 12 hours	1) SpTMs motor area (upper limbs); 2) Onset latency and MEPs amplitude; 5) MEPs dichotomized as present or absent without considering amplitude or onset latency	1) MEPs and GOS showed no significant correlation: 2) Bilaterally absent MEPs (n=5): 3 died, one VS, one severely disabled with severe tetraparesis
TMS in emergence from coma						
Moosavi *et al.* /71/	T (n=12) NT (n=7)	Consistently unresponsive (n=11) or minimally responsive (n=8); clinical agreement, standard score NA	TMS and clinical examination: 6-76 months after injury	Parkinsonism (n=2); Analgesic (n=5); Spasticity (n=14); Epilepsy prophylaxis (n=6); Depression (n=3);	1) Sp TMS motor area (upper limbs); 2) Onset latency and MEP amplitude	1) MEPs responses in 17 patients; 2) MT and latency within the normal range

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Reference	Aetiology*[1]	Level of consciousness*[2]	TMS interval*[3]	Drugs used	TMS paradigm	Main results
Crossley *et al.* /20/	T (n=1)	WHIM = 42 (eyes open briefly, attention held momentarily by dominant stimulus)	TMS + clinical examination: 4 weeks post injury and 1 year post injury	NA	1) SpTMS motor (upper limbs); 2) Onset latency and MEP amplitude	1) Increase in MEPs amplitude 2) MEPs correlated with clinical improvement
Barba *et al* /6/	T (n=1)	GCS 4 (admission), coma (15 days); Level of consciousness: fully awake Motor: mild left hemiparesis (able to use left hand in daily life)	TMS + clinical examination: 3 moths post injury	NA	1) SpTMS motor area (upper limbs); 2) MT 3) Mapping motor cortex (area and volume)	TMS correlated to clinical examination: MT right hemisphere (82%) versus left hemisphere (62%); right-left asymmetry in the motor maps
TMS in LIS						
Bassetti *et al.* /8/	NT (n=6)	Complete LIS (n=4); Horizontal eye movements (n=2)	TMS: acute (n=6); Follow-up: one year (n=1); four years (n=1)	NA	1) SpTMS motor area (upper and lower limbs); 2) Onset latency and MEPs amplitude; 3) Painful stimuli to induce some reaction (in the face)	1) MEPs absent in four patients: no one recovered clinically (death n=2, chronic LIS n=2); 2) MEPs present n=2 : good recovery; 3) MEPs reappearance on follow-up (n=2)
Cincotta *et al.* /18/	NT (n=1)	Blink and vertical eye movement on command	TMS + clinical examination: 1 month, 2 months; 22 months Death: 26 months due to a cardiac arrest	NA	1) SpTMS motor area (upper and lower limbs); 2) Onset latency and MEPs amplitude; 3) Motor imagery task	1) MEPs only left upper and lower limb; 2) Motor imagery: decrease latency, increase MEPs left upper limb; 3) Reappearance of MEPs, although no clinical recovery occurred

*[1] Aetiology of coma: T = traumatic brain injury, NT = non-traumatic brain injury (included diagnoses as anoxia/hypoxia, subarachnoidal haemorrhage, intracerebral haemorrhage, and other non-specified non-traumatic origin); *[2] Time when evaluation of level of consciousness was performed; *[3] Interval between coma onset and TMS examination; *[4] Only patients with brainstem lesions were included; NA = not reported in the study; TMS = transcranial magnetic stimulation; spTMS = single pulse TMS; MEP = motor evoked potential; MT = motor threshold; GCS = Glasgow Coma Scale; WHIM = Wessex Head Injury Matrix (a 62-item assessment tool that rates both spontaneous behaviours and responses to naturally occurring and standardized stimuli: begins with items measuring arousal and alertness (e.g. eyes open briefly; attention held momentarily by dominant stimulus) and ends with items reflecting language and memory functions (e.g. initiates conversation; remembers something from the day before); GOS = Glasgow Outcome Scale: GOS V = death; GOS 4 =VS; GOS 3 = severely disabled; GOS 2 = moderate deficit; GOS 1 = good recovery.

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Scale (GOS) three months and two years later. Thirteen out of 18 patients with bilaterally absent magnetically elicited MEPs were either dead or remained in VS. In the group of seven patients with normal onset of MEPs bilaterally, two patients showed good recovery, one patient died and one patient remained in VS. In 14 patients with bilaterally preserved but delayed or unilaterally absent MEPs, six were dead or remained in VS and no good recovery occurred. The results from electrically elicited MEPs showed that 37 (100%) patients with absent MEPs died, 23 (70%) patients with unilaterally absent MEPs and 62 (43%) patients with bilaterally either normal or delayed MEPs died or remained in VS. Twenty-nine (16%) patients showed good recovery if the MEPs were preserved on at least one side. These results lead to the conclusion that the presence of MEPs (elicited either electrically or magnetically) offers no prognostic value, and only bilateral absence of electrically elicited MEPs may be an unfavourable prognostic sign. The better predictive value of absent electrically but not magnetically elicited MEPs could be explained by the different mechanisms of motor cortex activation by these two techniques. As the transcranial electrical stimulation activates the pyramidal cells directly, TMS is thought to activate the neurons transsynaptically /24/. When cortical excitability is decreased, the single magnetic stimulus might not be strong enough to excite the motor cortex due to the higher threshold for activation of the underlying neurons. Another study of clinical and predictive value spTMS evoked MEPs was done by Schwarz *et al.* /89/ in 30 intensive care patients with acute brainstem lesions immediately after emergency treatment. Ten patients were reported to be comatose, twelve stuporous, seven somnolent and one fully awake at the time of MEP recordings. The outcome was assessed using the COS three months later. Four out of five patients with bilaterally absent MEPs showed poor recovery (either death or VS); one remained severely disabled. In the group of 25 patients with bilaterally or unilaterally preserved MEPs, five had died or remained in VS, and 20 had moderate or severe disability. This study supports the previous findings that magnetically evoked MEPs have a very limited prognostic value.

In summary, TMS allows no prognostic conclusion regarding the consciousness outcome. MEPs may be useful in assessment of comatose patients, especially with the purpose of defining more precisely the degree of motor impairment, but the conclusion that TMS can provide additional information as compared with clinical examination alone remains controversial.

TMS IN VS AND MCS

Moosavi *et al.* /71/ applied spTMS to the hand and leg motor area in 19 patients with severe brain injury either anoxic (n=7) or traumatic (n=12). The study was conducted 6-76 months after injury; eleven patients were consistently unresponsive to simple verbal commands and multimodality sensory stimulation, and eight patients could respond with reliable movements such as gaze directed selection of "yes" or "no" signs. No patient was able to make isolated finger or thumb movements. Despite the absence of voluntary movements, TMS elicited MEP responses in 17 out of the 19 severely brain damaged patients. Two of eight minimally responsive patients lacked MEPs on one side of the body but did have responses on the other side. In two of the eleven unresponsive patients it was impossible to elicit MEPs in any muscle. Whether the absence of MEPs can be attributed to the focal damage in the respective motor areas remains speculative as the authors do not present any imaging data on these patients. The responses in the group of non-responsive and in the group of minimally responsive patients differed in having a higher threshold, longer duration, and greater irregularity in the form of the response. On the other hand, the threshold, form and latency of the MEPs were similar in the normal subjects and minimally responsive patients. These results support the idea that a degree of cortical functional integrity is present in patients clinically diagnosed as being in MCS /56/. Mazzini *et al.* /66/ conducted a study to monitor recovery from severe traumatic brain injury. These authors examined MEPs from upper and lower limbs in 27 patients with decreased consciousness (GCS ranged from six to ten) in the subacute period (mean 2 months after

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injury), and 6 and 12 months later. Five patients remained VS one year after the trauma and one died at the end of the follow-up. During the study period the authors observed a trend toward an increase of amplitude and decrease of latency of MEPs. MEPs from upper and lower limbs progressively normalized in all patients, and at one year after trauma only 12% of patients had mild abnormalities. The differences between basal MEP scores and those at 12 months after trauma did not correlate with the GCS at the time of injury and the duration of coma. With regard to the prognosis, measured by GOS, no correlation was found.

Another two case reports were published with the aim of describing recovery from coma using a multimodal assessment including also spTMS. In the first one, Crossley *et al.* /20/ described the relationship between cognitive and behavioural ability and spTMS elicited MEPs. In their study recovery from coma was monitored using the Wessex Head Injury Matrix /92/. Clinical and TMS examinations were performed at four weeks post injury, when the patient showed signs of arousal and alertness (eyes open briefly, attention held momentarily by dominant stimulus), and 12 months later, when the patient was reported to be fully awake. The amplitude of the MEP response and onset latency was measured. TMS conducted at 12 months showed an increase in MEP amplitude in comparison to the recording at 4 weeks, consistent with clinical improvement. The second study /6/ focused on the ability of TMS to detect dysfunction of the motor cortex despite the absence of any detectable morphological lesion on several magnetic resonance images in a patient who emerged from coma due to traumatic brain injury three months after the trauma and presented left hemiparesis. TMS mapping of the motor area (number of scalp positions from which MEPs can be elicited and sum of the averaged MEP amplitude from each excitable scalp position) demonstrated a lower excitability of the cortical representation of the affected hand compared to the excitability of the "healthy" side.

These data suggest that TMS measures may be useful in the assessment of functional connectivity in the motor cortex in patients with severe motor disability and in motoring motor function recovery.

TMS IN LIS

Two studies are available on spTMS in LIS patients. The first one was done by Bassetti *et al.* /8/, who reported MEP recordings from both upper and lower limbs in six patients with LIS. MEPs were absent in four patients, none of whom recovered clinically (two patients died within one week after onset of LIS, two other patients remained in chronic LIS one year after the insult); in two patients, MEPs could be obtained from the severely paretic limbs, and almost full motor recovery followed. These findings are in agreement with a study which shows that the absence of response to TMS in the first hours after ischemic stroke is predictive of absent or very poor, not useful, hand motor recovery /77/. The second study evaluated spTMS evoked MEPs in a case of LIS due to a large pontine infarction /18/.One month after the attack no MEPs could be recorded from either the right upper or lower limb. On the contrary, MEPs were obtained from the left hand, although with a prolonged latency and reduced amplitude. When the patient was requested to mentally perform an abduction of her paralyzed left little finger, the latency and the amplitude of these responses improved as compared with the relaxed condition. Although in this patient no control condition was investigated to rule out the possibility that MEP changes could depend on general arousal effect, it seems reasonable to conclude that motor imagery played a major role in determining this facilitation.

These studies support the value of TMS in the assessment of motor function and prediction of motor outcome, but the sensitivity in LIS patients needs to be explored in larger studies.

FUTURE DIRECTIONS

Most previous studies investigated magnetically elicited MEPs as a potential prognostic marker, but the overall results show that MEPs fail to predict the outcome in severe brain injury. One of the limitations of the classical magnetically evoked MEPs in clinical settings appears to be its absence in some patients with good outcome. In contrast,

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abolition of cortical sensory evoked potentials have 100% prognostic specificity for non-awakening in comatose patients secondary to anoxic-ischemic injury and 87-99% specificity in predicting poor outcome in traumatic coma (reviewed in /102/). A transient absence of MEPs in comatose patients may be due to reversible damage of motor pathways or decreased excitability due to treatment (e.g. sedation, antiepileptic drugs). At least three potential hypotheses could explain the lack of prognostic value of TMS in previous reports: (a) methodological differences in grading of MEP abnormalities; (b) TMS stimulation paradigms (only spTMS was used by all authors, and standardized facilitation paradigms in unresponsive patients is lacking); (c) ill-defined consciousness impairment in patient populations. When cortical excitability is decreased, the single magnetic stimulus might not be strong enough to excite the motor cortex even with the maximal stimulator output; therefore facilitation techniques should be applied in comatose patients. As the commonly used technique of voluntary muscle contraction in healthy volunteers is not possible in unresponsive patients, other more promising means of modulating motor cortical excitability (e.g. premotor stimulation, theta burst, stimulation with repetitive paired pulse TMS) have to be used.

Structural brain imaging studies demonstrate that the behavioural level ultimately achieved by a patient following severe brain injury cannot be simply graded by the degree of diffuse axonal and direct ischemic brain damage /41/. Changes in cerebral metabolism and in the excitability of brain areas remote from a lesion have been reported in animals and humans and implicated as mechanisms relevant for functional recovery /5,90/. The underlying mechanisms of these observations involve the unmasking of existing, but latent, horizontal connections /83/ or modulation of synaptic efficacy such as long-term potentiation or long-term depression /19/. The neurotransmitter systems involved in mediating these effects include the inhibitory GABAergic /45,46/ as well as the excitatory glutamatergic system with activation of N-methyl-D-aspartate (NMDA) receptors /44/. TMS has been very useful in understanding the mechanisms underlying functional brain reorganization after stroke associated either with spontaneous recovery /12,22,36,59,63/ or following neurorehabilitation /17,42,57/. Similar TMS studies in disorders of consciousness may provide more knowledge about the pathophysiology and recovery from these conditions, which will increase our possibility for more accurate prognosis and will improve treatment. Paired-pulse and repetitive stimulation paradigms might identify signs of preserved brain connectivity in non-communicative brain damaged patients. Transcallosal inhibition and short latency afferent inhibition are worth exploring in patients with disorders of consciousness as they are potent connectivity markers. On the other hand, as motor imagery is shown to facilitate MEP responses even in the case of total muscle paralysis /18/, this stimulation paradigm could be further explored in MCS and LIS patients. If motor imagery is shown to elicit MEP facilitation reliably, it could be used with the purpose of evaluating the patient's ability to understand and follow instructions.

We also suggest that repetitive TMS of brain areas other than the motor cortex could be evaluated as a potential treatment with the main goal of modulating the activity of some cortical-subcortical networks involved in the pathophysiological mechanisms of disorders of consciousness /55,56,75,85,86/. As focusing the magnetic field directly into the brain areas located deep below the scalp (e.g. hippocampus, thalamus, amygdala) remains impractical at present, it is encouraging to evaluate the possible therapeutic benefits of the stimulation of the brain areas other than the motor cortex, which may play a role in the attention, memory and speech processes, such as dorsolateral prefrontal cortex /11,80/, fronto-parietal /43, 52,72/, posterior-parietal /82/, and Wernicke's area /3/. The respective value of different invasive /84/ and non-invasive /91/ methods of cortical stimulation also remains to be determined in this challenging group of patients.

CONCLUSION

We anticipate that TMS will not give definite answers about prediction of motor or consciousness outcome in coma, VS, MCS, and LIS, but rather

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that it will extend our understanding of the underlying mechanisms of these disorders. Use of this technique in severe brain damage remains methodologically vague and must be further validated prior to clinical application in these challenging patients. At presence, the field of neurorehabilitation lacks evidence-based treatment in the disorders of consciousness, and TMS could help to measure objectively the effect of pharmacological and non-pharmacological therapeutic interventions. Finally, the medical community needs to define the ethical framework permitting study of brain function and plasticity in these non-communicative severely brain damaged patients, by definition unable to provide consent.

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QUE MESURE LA NEURO-IMAGERIE FONCTIONNELLE : IRMf, TEP & MEG ?

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RÉSUMÉ : Les techniques d'imagerie fonctionnelle cérébrale (IFC) étudient *in vivo* le fonctionnement du cerveau humain dans des conditions physiologiques ou pathologiques. Elles permettent d'identifier les réseaux neuronaux impliqués dans diverses tâches psychomotrices. Cet article décrit trois techniques d'IFC fréquemment utilisées en recherche en neuroscience et en clinique : l'imagerie par résonance magnétique fonctionnelle (IRMf), la tomographie par émission de positons (TEP) et la magnétoencéphalographie (MEG). L'IRM et la TEP mesurent les changements hémodynamiques régionaux induits par les variations de l'activité neuronale. Ces deux techniques possèdent une haute résolution spatiale (quelques millimètres), mais une résolution temporelle relativement médiocre (quelques secondes à plusieurs minutes). L'électroencéphalogramme (EEG) et la MEG mesurent l'activité électromagnétique neuronale avec une très haute résolution temporelle (de l'ordre de la milliseconde), mais avec une résolution spatiale plus faible (de quelques millimètres à un centimètre). L'intégration de ces différentes techniques d'IFC permet, en combinant ces différents aspects (couplage neurovasculaire, activité électromagnétique), d'étudier le fonctionnement cérébral avec une haute résolution temporelle et spatiale.

Mots-clés : ***Neuro-imagerie fonctionnelle - Imagerie par résonance magnétique - Tomographie par émission de positons - Magnétoencéphalographie - Intégration multimodale***

Functional neuroimaging (fMRI, PET and MEG) : what do we measure ?

SUMMARY : Functional cerebral imaging techniques allow the *in vivo* study of human cognitive and sensorimotor functions in physiological or pathological conditions. In this paper, we review the advantages and limitations of functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG). fMRI and PET measure haemodynamic changes induced by regional changes in neuronal activity. These techniques have a high spatial resolution (a few millimeters), but a poor temporal resolution (a few seconds to several minutes). Electroencephalogram (EEG) and MEG measure the neuronal electrical or magnetic activity with a high temporal resolution (i.e., milliseconds) albeit with a poorer spatial resolution (i.e., a few millimeters to one centimeter). The combination of these different neuroimaging techniques allows studying different components of the brain's activity (e.g., neurovascular coupling, electromagnetic activity) with both a high temporal and spatial resolution.

Keywords : ***Functional neuroimaging - Magnetic resonance imaging - Positron emission tomography - Magnetoencephalography - Multimodal integration***

Introduction

A l'heure actuelle, les méthodes de neuro-imagerie fonctionnelle sont largement utilisées à travers le monde, tant au niveau clinique que dans la recherche scientifique. Si le développement de ces techniques a commencé il y a seulement quelques dizaines d'années, les bases sur lesquelles elles reposent sont bien plus anciennes. D'un point de vue historique, la première manière d'explorer le fonctionnement du cerveau était de le disséquer en post-mortem et de réaliser des corrélations anatomocliniques. Grâce aux avancées technologiques, il est désormais possible d'étudier *in vivo* le fonctionnement du cerveau dans des conditions physiologiques ou pathologiques.

A la fin du 19ème siècle, le physiologiste italien Angelo Mosso observa fortuitement une relation entre le débit sanguin cérébral et l'activité neuronale en étudiant les pulsations cérébrales chez un traumatisé crânien (1). Lorsque Mosso demanda au patient d'effectuer une tâche de calcul mental, il observa une augmentation des pulsations cérébrales et du débit sanguin. Cette observation a été la première à suggérer que la mesure du flux sanguin cérébral pouvait être un moyen d'évaluer la cognition humaine.

Plus tard à l'Université de Cambridge, Charles Roy et Charles Sherrington ont précisé cette relation entre activité neuronale et flux sanguin cérébral. Se basant sur des expériences animales, ils ont suggéré que le cerveau possède un mécanisme intrinsèque par lequel le débit sanguin peut varier localement en fonction des variations locales de l'activité neuronale (3). Un des plus extraordinaires exemples de cette relation a été observé chez Walter K, un marin qui se plaignait d'entendre un bourdonnement. Le médecin qui l'examina confirma la présence de ce bruit anormal en plaçant un stéthoscope à l'arrière de la tête du patient. Walter K. présentait en fait une

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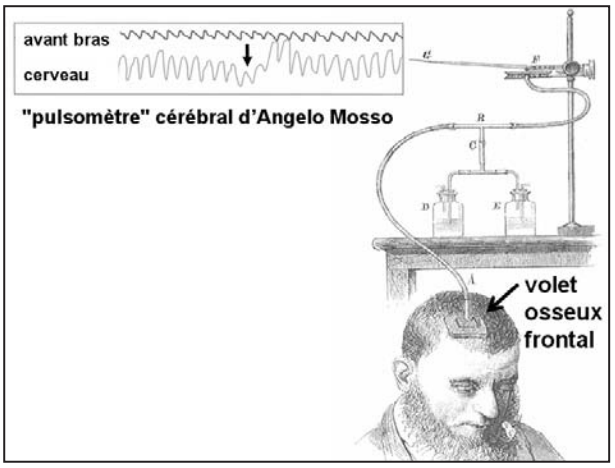


Figure 1. Première étude de «neuro-imagerie fonctionnelle». Le «pouls cardiaque» du cerveau enregistré lors de récit intérieur (réciter silencieusement un «avé maria»; indiqué par la flèche) (1881) adapté de Posner et Raichle (1994) (2).

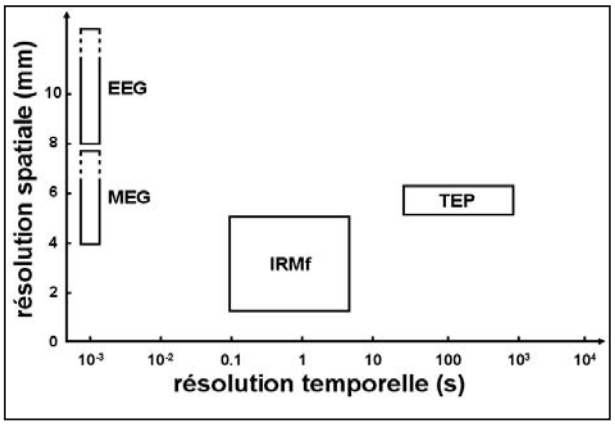


Figure 2. Résolutions temporelle et spatiale des techniques d'imagerie fonctionnelle cérébrale les plus communément utilisées. Adapté de Laureys et al (2002) (13).

large malformation artérioveineuse au niveau du cortex visuel. Lorsqu'il stimulait son cortex visuel, par exemple en lisant un journal, l'intensité du bruit augmentait et lorsqu'on diminuait le niveau de stimulation du cortex visuel, par exemple dans l'obscurité, le bruit disparaissait après deux minutes (4). Les recherches récentes utilisant la tomographie par émission de positons (TEP) qui permet d'étudier les variations du débit sanguin cérébral ont fourni une remarquable confirmation des observations de ces pionniers (5, 6).

La résonance magnétique nucléaire (RMN) fut développée par Félix Bloch et Edward Mills Purcell qui reçurent le prix Nobel de physique en 1952. La résonance magnétique a d'abord été employée en spectroscopie, technique qui permet d'obtenir des informations sur la composition chimique des substances. L'idée de créer des gradients dans le champ magnétique pour déterminer l'endroit d'origine des ondes électromagnétiques émises par les noyaux des atomes a été attribuée à Paul C. Lauterbur qui reçut le prix Nobel de physiologie en 2003. Cette information spatiale a permis de reconstruire des images bidimensionnelles rendant possible le développement de l'IRM. La technique a ensuite été adaptée pour mesurer les variations d'oxygénation du sang, reflet indirect de l'activité neuronale. On parle alors d'IRM fonctionnelle (IRMf).

Berger (7) est, quant à lui, le premier à avoir établi un lien entre la variation de l'activité électrique cérébrale et l'état fonctionnel du cerveau. Grâce au développement d'électrodes de scalp et de l'EEG, il est devenu possible d'enregistrer les variations de l'activité électrique neuronale spontanée physiologique ou pathologique ainsi que les potentiels électriques évoqués par différentes tâches psychomotrices. De nombreuses études ont démontré que la variété et la complexité des différents rythmes enregistrés par l'EEG sont inversement corrélés à la sévérité du dysfonctionnement cérébral (8). Par la suite, la magnéto-encéphalographie (MEG) a été développée afin d'étudier les variations non plus de potentiel électrique mais de champs magnétiques résultant de l'activité électrique neuronale.

La contribution de ces différentes techniques d'imagerie fonctionnelle cérébrale (IFC) à la recherche en neuroscience et à la pratique clinique est devenue fondamentale. Non seulement ces techniques fournissent des images de haute résolution des structures nerveuses (imagerie anatomique) permettant la démonstration de lésions cérébrales, mais elles rendent également possible l'étude du fonctionnement cérébral (imagerie fonctionnelle). Par exemple, les techniques d'IFC permettent d'identifier les réseaux neuronaux impliqués dans diverses tâches psychomotrices et d'investiguer les phénomènes de plasticité induits par une pathologie neuropsychiatrique donnée.

Dans cet article, nous envisagerons les techniques d'IFC que sont l'IRMf, la TEP et la MEG. L'EEG, plus classique, ne sera abordé que pour le comparer à la MEG. Pour chaque technique envisagée, nous exposerons d'abord les principes sur lesquels elle s'appuie. Ensuite, nous décrirons les procédés d'instrumentation et nous résumerons leurs propriétés en termes de résolution spatiale et temporelle. Nous discuterons enfin de leurs avantages et de leurs limites et suggérerons que l'utilisation multimodale est la clé de l'utilisation optimale de ces outils récents.

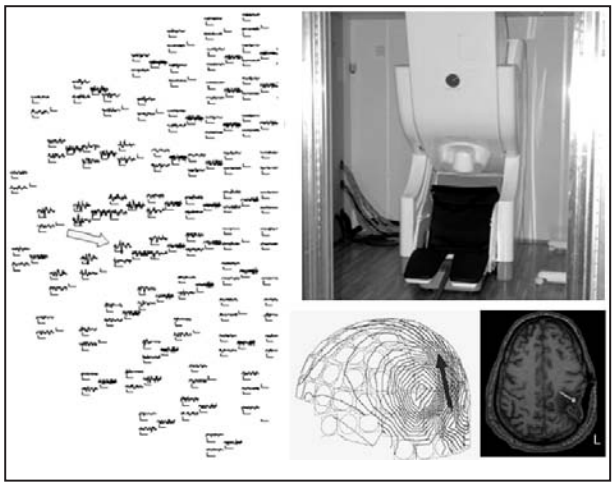


Figure 3. Droite, haut : Photographies du système MEG Elekta-Neuromag Vectorview 306 installé dans l'Unité MEG de l'Hôpital Erasme (Bruxelles, Belgique). Gauche : Moitié gauche de la représentation 2D des senseurs MEG montrant 200 ms de données MEG continues. La flèche indique l'amplitude maximale d'une pointe épileptique intericale. Droite, bas : Champs magnétiques correspondant à l'amplitude maximale de la pointe épileptique intericale superposés à la représentation du casque des senseurs MEG (vue gauche). La flèche représente le dipôle de courant équivalent expliquant le mieux les champs magnétiques correspondants. Imagerie par source magnétique : dipôle de courant équivalent co-registré sur l'IRM 3D T1 du patient pour localiser de manière précise la zone épileptogène

IRM

PRINCIPE DE BASE

L'IRM structurelle a révolutionné les neurosciences cliniques en permettant d'obtenir *in vivo* des images anatomiques de très haute résolution améliorant ainsi le diagnostic des lésions cérébrales ainsi que l'étude des réorganisations anatomiques qu'elles induisent. L'IRM fonctionnelle (IRMf) a, quant à elle, été développée pour étudier le fonctionnement cérébral régional.

Le principe sur lequel se base l'IRMf est que les neurones impliqués dans une tâche psychomotrice augmentent leur niveau d'activité lors de la réalisation de cette tâche ce qui nécessite d'accroître l'apport en énergie et en oxygène. La vascularisation cérébrale répond à cette demande en augmentant localement le débit sanguin. C'est le classique couplage neurovasculaire. Les neurones activés ne consomment toutefois pas la totalité de l'oxygène apporté à la suite de cette augmentation locale de perfusion. Ceci, comparé à la situation de repos, entraîne une modification du rapport entre les taux d'hémoglobine oxygénée (oxyHb) et déoxygénée (déoxyHb) en défaveur de la déoxyHb. Cette modification du rapport oxy-/déoxyHb au sein de la région cérébrale activée est à l'origine de l'effet BOLD (Blood Oxygenated Level Dependent) qui est le signal détecté en IRMf. En effet, l'oxyHb et la déoxyHb se comportant différemment dans un champ magnétique, la modification de leur rapport va induire des inhomogénéités de champ magnétique qui vont pouvoir être détectées par IRM. L'acquisition ultrarapide d'images du cerveau par IRM permet ainsi d'étudier les variations du signal BOLD en réponse à une tâche donnée et d'identifier le réseau neuronal impliqué dans cette tâche.

Le signal d'intérêt étudié par IRM au niveau des tissus est produit en réponse à des impulsions d'ondes électromagnétiques générées par une «bobine» (transmitter coil) qui recouvre l'entièreté ou une partie du corps («head coil»). Ces impulsions génèrent des variations spatiales très brèves (gradients) de la puissance du champ magnétique généré par l'aimant principal au sein des tissus, ce qui modifie le niveau d'énergie des noyaux atomiques (moment magnétique nucléaire). Lorsque la fréquence de l'onde électromagnétique utilisée permet d'obtenir cette transition du niveau d'énergie des atomes, les atomes qui étaient en état de faible énergie passent en état de haute énergie; c'est le phénomène de résonance. Lorsque les impulsions s'arrêtent, les atomes retournent à leur état initial de faible énergie en émettant eux-mêmes un signal électromagnétique à une fréquence donnée qui peut être détectée par des capteurs; c'est le phénomène de relaxation. L'intensité du signal émis par les atomes est directement proportionnelle à la quantité d'atomes présents dans le tissu analysé. Les atomes d'hydrogène ayant un moment magnétique non nul (c'est-à-dire la grandeur vectorielle qui permet de mesurer l'intensité d'une source magnétique) (comparé par exemple au carbone 12 et à l'oxygène 16), c'est la résonance magnétique de l'hydrogène (proton) qui est le plus utilisée.

INSTRUMENTATION

L'IRM est un appareil constitué d'un aimant superconducteur permanent d'une puissance variant de 0,5 Tesla jusqu'à 7 ou 8 Tesla. Cette technique est considérée comme non invasive car elle n'utilise pas de radiation ionisante. Le terme nucléaire fait, en effet, référence aux noyaux atomiques et non à des phénomènes de radioactivité. L'acquisition de données IRM au niveau cérébral nécessite l'utilisation d'une bobine spéciale («head coil») qui va permettre d'obtenir les gradients de champs magnétiques.

RÉSOLUTIONS TEMPORELLE ET SPATIALE

L'augmentation du flux sanguin au niveau de la région cérébrale activée suit une cinétique particulière qui est modélisée par la fonction de

réponse hémodynamique. En effet, le couplage neurovasculaire prend cinq à six secondes pour atteindre son maximum. C'est pourquoi, l'acquisition rapide d'images du cerveau par IRM permet de suivre l'évolution du signal BOLD en réponse à une activité psychomotrice donnée. La séquence IRM utilisée pour l'IRMf s'appelle «Echo Planar Imaging» (EPI) et permet d'obtenir des images du cerveau complet (volume cérébral) en quelques secondes, typiquement 2 à 3 secondes. L'IRMf permet donc d'étudier le fonctionnement neuronal avec une résolution temporelle de l'ordre de la seconde. La résolution spatiale de l'IRMf est de l'ordre de quelques millimètres. Un moyen d'améliorer la puissance de la technique est d'augmenter l'intensité du champ magnétique (en passant de 1,5 Tesla à 7 ou 8 Tesla). Des champs magnétiques plus intenses permettent d'augmenter la résolution spatiale et d'améliorer la résolution temporelle en permettant la détection des différentes phases de la réponse hémodynamique.

TEP

Principe de base

La TEP a été développée pour mesurer différents aspects de la physiologie des fonctions cérébrales en fonction du type de traceur radioactif utilisé. Le métabolisme glucidique, la synthèse des protéines et la distribution des récepteurs sont des exemples de fonctions étudiées par la TEP. Le débit sanguin, le volume sanguin et la consommation d'oxygène peuvent également être mesurés par TEP et ce, à nouveau dans le contexte des variations hémodynamiques associées à l'activité neuronale (9).

La TEP implique l'administration par injection intraveineuse d'un traceur radioactif émetteur de positons (e+) à courte demi-vie. Dans les tissus, les positons émis se combinent immédiatement avec un électron (e-) et s'annihilent réciproquement en produisant deux photons γ à haute énergie émis dans des directions opposées. La détection de cette paire de photons γ est à la base de l'imagerie TEP. En effet, le tomographe est constitué d'un cercle de détecteurs pouvant détecter ces photons d'annihilation en coïncidence, ce qui permet d'identifier leur origine. A partir de ces informations, un algorithme de reconstruction reconstitue une image de la répartition du traceur sous la forme d'images 2D ou 3D. Lors de la traversée du corps, les photons γ peuvent subir une atténuation liée aux structures traversées (p.e. l'os). Il est donc nécessaire de réaliser une correction pour tenir compte de ces paramètres d'atténuation. Cette correction est effectuée à partir d'images de transmission obtenues grâce à une source radioactive externe qui irradie le sujet permettant ainsi de mesurer le facteur d'atténuation des rayons ionisants.

Le type d'information des images TEP est fonction du traceur radioactif injecté. L'Oxygène-15, le fluor-18, et le carbone-11 sont les radio-isotopes les plus utilisés qui peuvent être intégrés dans diverses molécules organiques telles que les molécules d'eau, le glucose ou divers agonistes ou antagonistes de récepteurs cérébraux.

Pour les études d'activation cérébrale qui nous intéressent dans cet article, la TEP est actuellement supplantée par l'IRMf et ce, principalement à cause de son côté invasif (irradiation, injection intraveineuse) et de sa plus faible résolution temporelle. Pour ce type d'étude, la TEP utilise de l'eau marquée à l'oxygène-15 et étudie les variations de la distribution régionale de la radioactivité induites par le couplage neurovasculaire. Dans le domaine des neurosciences, la TEP reste toutefois une technique d'IFC très utilisée tant en clinique (cancérologie, épilepsie, maladies inflammatoires, etc.) qu'en recherche (étude du métabolisme cérébral, étude de la distribution des récepteurs, etc.).

Instrumentation

La TEP nécessite de disposer de traceurs émetteurs de positons, ce qui implique d'avoir accès à un cyclotron. Le tomographe a l'aspect d'un scanner ou d'une IRM et est constitué de plusieurs couronnes ou cylindres de cristaux sensibles aux photons γ. Il possède également des sources radioactives (césium, germanium, etc.) pour réaliser l'image de transmission. L'évolution récente de la TEP est le couplage de cette technique d'imagerie fonctionnelle avec le scanner à rayons X («PET-CT») dans le but de permettre un repérage anatomique précis des anomalies métaboliques révélées par la TEP. Dans ce contexte, l'imagerie de transmission est réalisée par le scanner. Enfin, la combinaison de la TEP avec l'IRM est en cours de développement dans différents centres et représente sans doute l'avenir de la TEP.

Résolutions spatiale et temporelle

Typiquement, la TEP permet de localiser les changements dans l'activité cérébrale avec une précision spatiale de l'ordre de 5 à 10 mm^3 ce qui représente l'activité de plusieurs milliers de cellules. La résolution spatiale est donc inférieure à celle que celle de l'IRMf mais reste de

l'ordre de quelques millimètres. La résolution temporelle est quant à elle relativement faible puisqu'il faut une à plusieurs minutes pour obtenir une seule image TEP.

MEG

PRINCIPE DE BASE

La MEG mesure les variations des champs magnétiques produits par les courants ioniques principalement générés par les potentiels postsynaptiques des cellules pyramidales du cortex cérébral. Contrairement aux champs électriques enregistrés par EEG, les champs magnétiques ne sont pas sensibles aux variations de conductivité, ni à l'anisotropie ce qui explique qu'ils ne sont pas altérés par les différentes couches (liquide céphalo-rachidien, méninges, os, graisse, peau) qu'ils doivent traverser pour gagner la surface du crâne. Les relations physiques qui unissent les champs électriques aux champs magnétiques sont définies par les équations de Maxwell. La MEG est principalement sensible aux dipôles électriques qui sont orientés parallèlement à la surface du crâne. En effet, seuls ces dipôles électriques vont pouvoir donner naissance à un champ magnétique mesurable à l'extérieur de la tête. Puisque les dendrites des cellules pyramidales du cortex sont alignées de manière perpendiculaire à la surface du cortex, la MEG sera principalement sensible aux dipôles électriques localisés dans le cortex fissural (sillons et scissures corticales) qui représentent 2/3 de la surface corticale (10).

Le champ magnétique produit par un seul potentiel postsynaptique étant trop faible pour être détecté par la MEG, c'est l'activité synchrone de millions de neurones qui est mesurée (9). Les champs magnétiques produits par l'activité neuronale détectables par la MEG ont une intensité variant entre 10-12 et 10-15 Tesla, c'est-à-dire un champ magnétique beaucoup plus faible que le bruit magnétique environnant (champ magnétique de la terre, lignes électriques, etc.) (9). Dès lors, en fonction du rapport signal sur bruit des phénomènes d'intérêt (p.e. activité oscillatoire, activité paroxystique de type épileptique, champs magnétiques évoqués), il peut s'avérer nécessaire de moyenner l'activité magnétique cérébrale correspondant à des centaines d'événements d'intérêt (9).

Un des avantages de la MEG est de permettre la localisation des sources électriques à l'origine des champs magnétiques. Ceci nécessite toutefois d'enregistrer de pair données MEG et données structurelles obtenues par IRM. La combinaison de la MEG et de l'IRM s'appelle l'imagerie par source magnétique (ISM, «Magnetic Source Imaging»). La localisation de sources responsables du signal MEG enregistré nécessite de résoudre le problème inverse («inverse problem») qui consiste de manière simplifiée à rechercher la cause à partir de ses effets (9). Le problème inverse est considéré comme un problème mal posé («ill posed problem») car il n'a pas de solution unique; ceci est à l'origine de la complexité des modèles et algorithmes utilisés pour le résoudre (9). L'ISM est de plus en plus utilisée en clinique pour localiser les foyers épileptiques (Fig. 3) ou les régions cérébrales fonctionnellement importantes en vue d'une chirurgie. Elle est également utilisée en recherche pour déterminer la chronométrie d'activation des réseaux neuronaux impliqués dans des tâches diverses psychomotrices.

INSTRUMENTATION

Pour détecter des champs magnétiques de l'ordre du femto Tesla, la MEG utilise des senseurs de type SQUID (Superconducting Quantum Interference Device) qui possèdent des propriétés superconductives (résistance électrique égale à 0) lorsqu'ils sont maintenus à une température de l'ordre de -269 C° (9). Ceci nécessite que les SQUIDs soient plongés de manière constante dans l'hélium liquide pour garder leurs propriétés superconductives (9). Un très grand nombre de SQUIDs (de 100 à 306 senseurs) sont disposés autour de la tête dans un casque faisant partie intégrante du réservoir d'hélium (Fig. 3). Contrairement à l'EEG, les senseurs de la MEG ne sont donc pas collés sur le scalp des sujets. Puisque les champs magnétiques produits par l'activité cérébrale sont beaucoup plus faibles que le bruit magnétique environnant, il est nécessaire d'utiliser des systèmes d'atténuation du bruit. Un des systèmes les plus efficaces est de réaliser les enregistrements MEG dans une chambre blindée contre les champs électromagnétiques («Magnetic Shielded Room», Fig. 3) (9). D'autres techniques telles que certains types de designs de SQUID, des mécanismes de compensation actifs ou des algorithmes mathématiques peuvent également être utilisées (9).

RÉSOLUTIONS SPATIALE ET TEMPORELLE

La MEG est caractérisée par une excellente résolution temporelle qui est de l'ordre de la milliseconde. Cette résolution temporelle permet d'étudier avec une très grande précision la chronométrie du fonctionnement cérébral. La résolution spatiale de la MEG dépend des tech-

niques utilisées pour réaliser la co-registration avec l'IRM (localisation de points d'intérêts au niveau de la surface du crâne), des modèles utilisés pour résoudre le problème inverse et de la qualité des données MEG. Selon les études, la résolution spatiale de la MEG varie de quelques millimètres à un centimètre. Sa résolution spatiale est donc généralement considérée comme plus faible que les autres techniques d'imagerie fonctionnelle.

CONCLUSION

Les techniques d'IFC permettent d'étudier *in vivo* le fonctionnement du cerveau humain dans des conditions physiologiques et pathologiques. Couplées à des données anatomiques de haute résolution, elles permettent d'identifier les réseaux neuronaux impliqués dans les tâches psychomotrices d'intérêt. Considérant les bases théoriques sur lesquelles elles reposent, les techniques d'IFC décrites dans cet article possèdent chacune des avantages et des inconvénients, notamment en termes de résolution spatiale et temporelle.

L'IRMf apporte des informations au niveau anatomique et fonctionnel ce qui permet d'obtenir des cartographies précises du fonctionnement cérébral. Cependant, sa faible résolution temporelle comparée à celle de la MEG ne permet pas d'obtenir d'information précise sur la chronométrie du recrutement des aires cérébrales identifiées. De plus, le fait que cette technique soit dépendante du couplage neurovasculaire, et donne donc une information indirecte de l'activité neuronale, peut parfois compliquer l'interprétation des résultats obtenus dans les cas de pathologies. En effet, la présence de lésions cérébrales ou l'utilisation de certains médicaments peuvent modifier le couplage neurovasculaire et être à l'origine de faux négatifs ou de faux positifs en termes d'activation cérébrale.

Les études d'activations réalisées en TEP donnent des informations relativement similaires à l'IRMf en termes de cartographie cérébrale, mais au prix d'une irradiation et d'un caractère invasif plus prononcé. Même si l'IRMf et la TEP ne permettent pas d'obtenir d'informations précises sur la chronométrie des événements étudiés, elles permettent néanmoins d'étudier la connectivité cérébrale qui consiste à déterminer les relations que les différentes parties d'un réseau neuronal vont tisser entre elles. Dans ce cadre, grâce à sa meilleure résolution temporelle, les informations obtenues par l'IRMf surpassent de loin celles obtenues par la TEP.

L'EEG et la MEG sont des techniques non invasives qui mesurent l'activité électrique et magnétique générée par le cerveau avec une résolution temporelle inégalée. Elles donnent donc des informations directes sur l'activité neuronale en cours. Les principaux atouts de la MEG par rapport à l'EEG sont un nombre plus élevé de senseurs ainsi que l'absence de sensibilité aux variations de conductivité et à l'anisotropie, ce qui simplifie la résolution du problème inverse et explique la meilleure résolution spatiale de la MEG. De plus, la MEG est plus aisée à utiliser que l'EEG puisqu'elle ne nécessite pas de coller des électrodes. Les principaux désavantages de la MEG, par rapport à l'EEG, sont sa faible accessibilité principalement liée à son coût très élevé (achat du système, consommation importante d'hélium liquide) et le fait qu'elle est principalement sensible à l'activité neuronale du cortex localisée des sillons et non aux sources orientées radialement. De plus, elle a une plus grande sensibilité aux mouvements de la tête que l'EEG puisque les senseurs ne sont pas attachés sur la tête du sujet. Sur base de ces considérations théoriques, la plupart des auteurs s'accordent sur le fait que la MEG et l'EEG sont des techniques d'IFC complémentaires et non concurrentes. Enfin, à la différence des autres techniques comme l'IRMf ou la TEP, la MEG et l'EEG mettent difficilement en évidence les sources d'activité situées dans la profondeur du cerveau.

En conclusion, l'IRM et la TEP mesurent les variations hémodynamiques régionales secondaires aux modifications de l'activité neuronale induites par une tâche donnée. Elles donnent ainsi une information indirecte sur le niveau d'activité neuronale. Elles possèdent une haute résolution spatiale, mais une pauvre résolution temporelle. L'EEG et la MEG mesurent l'activité électromagnétique neuronale avec une très haute résolution temporelle, mais la localisation précise des sources de l'activité reste un problème méthodologique difficile à résoudre. La combinaison de ces mesures hémodynamiques et électromagnétiques représente donc une solution pour étudier les activations cérébrales avec une haute résolution spatiale et temporelle. Cette approche combinée permet d'exploiter les meilleurs aspects de chaque technique et offre une caractérisation plus complète des différentes facettes de l'activité cérébrale engagée dans les processus neurophysiologiques (11). Cependant, les avancées de l'intégration multimodale nécessitent encore d'améliorer les modèles de couplage entre les phénomènes physiologiques sous-tendant les différentes modalités du signal

(12). Ce type d'approche sollicite également beaucoup de ressources financières puisque les équipements IRM, TEP et MEG coûtent entre 1 et 4 millions d'euros et ont des frais de fonctionnement très élevés. L'intégration multimodale nécessite une collaboration efficace entre différentes équipes qui possèdent des expertises complémentaires afin d'optimiser l'utilisation des moyens.

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Electrophysiological investigations of brain function in coma, vegetative and minimally conscious patients

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Abstract:

Electroencephalographic activity in the context of disorders of consciousness is a swiss knife like tool that can evaluate different aspects of cognitive residual function, detect consciousness and provide a mean to communicate with the outside world without using muscular channels. Standard recordings in the neurological department offer a first global view of the electrogenesis of a patient and can spot abnormal epileptiform activity and therefore guide treatment. Although visual patterns have a prognosis value, they are not sufficient to provide a diagnosis between vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) patients. Quantitative electroencephalography (qEEG) processes the data and retrieves features, not visible on the raw traces, which can then be classified. Current results using qEEG show that MCS can be differentiated from VS/UWS patients at the group level.

Event Related Potentials (ERP) are triggered by varying stimuli and reflect the time course of information processing related to the stimuli from low-level peripheral receptive structures to high-order associative cortices. It is hence possible to assess auditory, visual, or emotive pathways. Different stimuli elicit positive or negative components with different time signatures. The presence of these components when observed in passive paradigms is usually a sign of good prognosis but it cannot differentiate VS/UWS and MCS patients. Recently, researchers have developed active paradigms showing that the amplitude of the component is modulated when the subject's attention is focused on a task during stimulus presentation. Hence significant differences between ERPs of a patient in a passive compared to an active paradigm can be a proof of consciousness. An EEG-based brain-computer interface (BCI) can then be tested to provide the patient with a communication tool. BCIs have considerably improved the past two decades. However they are not easily adaptable to comatose patients as they can have visual or auditory impairments or different lesions affecting their EEG signal.Future progress will require large databases of resting state-EEG and ERPs experiment of patients of different etiologies. This will allow the identification of specific patterns related to the diagnostic of consciousness. Standardized procedures in the use of BCIs will also be needed to find the most suited technique for each individual patient.

Keywords: electroencephalography, evoked related potential, brain computer interface, coma, vegetative state, unresponsive wakefulness syndrome, minimally conscious state, locked in syndrome

1. Introduction

The electroencephalography (EEG) has a long history of use in the intensive care unit, and there is a well documented literature on EEG abnormalities in comatose patients and patients in vegetative state (VS) or newly coined unresponsive wakefulness syndrome (UWS) (Laureys, Celesia et al. 2010). The use of EEG as a diagnostic tool is subject to controversies (Guérit 2007), but the prognostic value of EEG patterns when combined with the etiology is well acknowledged (Zandbergen, de Haan et al. 1998). However, the study of patients with disorders of consciousness (DOC) has experienced an important turn with the definition in 2002 of the minimally conscious state (MCS) as a state "characterized by inconsistent but clearly discernable behavioral evidence of consciousness and can be distinguished by coma and VS/UWS by documenting the presence of specific behavioral features not found in either of these conditions" (Giacino, Ashwal et al. 2002). This new definition has triggered the challenge to untangle VS/UWS and MCS patients. At bedside, behavioral scales such as the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar et al. 2004) are used to assess patients. This evaluation can give hints on the prognosis as MCS patients have better recovery chances than VS/UWS patients. Still, behavioral assessments are subjective and not always accurate (Schnakers, Vanhaudenhuyse et al. 2009) hence the need of objective multimodal assessments covering all aspects of brain functioning, ranging from the metabolism assessed with positron emission tomography (PET), the structural images captured with the magnetic resonance imaging (MRI), the hemodynamic response obtained with functional MRI, the structural changes in the white matter observed with diffusion tensor imaging (DTI) and the dynamics of cortical activations measured with EEG. In the following only EEG aspects of coma, VS/UWS and MCS patients will be covered as the other brain imaging methods are treated in detail in other papers of this issue.

Aside of standard clinical measurements, different applications have originated from EEG. For example, quantitative EEG (qEEG) consists in numerical computations of parameters from the EEG such as power spectra, connectivity values or entropy. These parameters offer better validity than visual scoring (Thatcher 2010) and subsequently they can be used to train classifiers in order to separate groups of patients in different states. Next, evoked potentials, allows the assessment of specific cortical functions by measuring responses to repeated given stimuli. Furthermore, the past twenty years have seen advances in the field of brain computer interfaces (BCI) using the EEG. Direct communication from the brain to a computer has been demonstrated (Wolpaw, Birbaumer et al. 2002; Birbaumer and Cohen 2007). Such devices can be of great help to assess consciousness in severe brain injured patients with DOC. In the following, standard clinical EEG patterns in coma and related states will be reviewed and illustrated. Second, the investigation of qEEG methods will be presented followed by a description of oscillatory brain activity in response to stimuli, i.e. event related potentials (ERPs). Finally, advances in brain computer interfaces and their applications at bedside will also be discussed.

2. Standard clinical EEG

The EEG is often mandatory in the neurological management. A routine clinical EEG recording lasts approximately seven to thirty minutes. Electrode failure and artifacts are common issues impeding the quality of the recording; hence its duration must be long enough to allow the practitioner to determine the background activity or main rhythm of the patient. Moreover, some physiologic or even pathologic events could be missed if the recording duration is too short. To unravel some of these features, clinical EEG often involve provocative tests such as photic, auditory or painful stimulation.

Visual inspection of the EEG traces can give insights on the origin and severity of the encephalopathy. First of all the clinician must identify the predominant rhythm. Healthy wake adults display at rest a posterior and symmetric alpha rhythm which oscillates between 8 and 12 Hz depending on the subject. The amplitude of the alpha rhythm increases when the eyes are closed and decreases in case of stress. The distribution and amplitude of the alpha rhythm can differ between individuals, some do not exhibit any alpha rhythm (approximately 2 % of the world population (Schomer 2007)), others might have an alpha rhythm of low amplitude. While most individuals have an alpha rhythm mainly distributed over posterior regions, in some subjects it can be concentrated on occipital leads and in others it might be more widely distributed (Niedermeyer and Da Silva 2005). An irregular beta rhythm (13-30 Hz) of smaller amplitude can be superimposed on the alpha rhythm, especially when the eyes are opened or when the subject is attentive to the environment. Those beta rhythms are also often present in case of benzodiazepine intake. When the subject is tired and drowsy, slower waves appear, and theta (4-7Hz) becomes the predominant rhythm. In deep sleep states, the predominant rhythm is delta (0.5-4Hz) (see Figure 1.I, 1.II and 1.III for alpha, theta and delta waves).

Following a brain injury, whether it is of traumatic or anoxic origin, the EEG can be altered and display abnormalities. A visible main effect is a slowing of the brain activity proportional to the severity of the injury. If cerebral suffering is diffuse, the predominant rhythm is no longer posterior alpha but diffuse theta or delta. In some cases of severe brain lesions alpha or theta activity can be observed but it does not resemble a normal adult alpha activity as it is frontally distributed and not reactive to stimuli such as eye opening or closing. These rhythms are coined alpha-coma or theta-coma (Kaplan, Genoud et al. 1999) (see Figure 1.VII for an illustration of alpha coma). Along with the diffuse slowing commonly observed in DOC patients, several additional patterns have been reported. In case of supratentorial lesions, polymorphic focal delta rhythm can be visible over the damaged regions (Brenner 2005). If there is asymmetric brain damage, the EEG will likely also be asymmetric; the electrogenesis of one hemisphere can appear almost normal whereas that of the other is severely impaired. Still a precise location of a lesion cannot be achieved with the EEG as its spatial resolution is low. When the lesions are infratentorial, the EEG can display a close to normal activity as it is sometimes but not always the case in locked-in patients (LIS) (Markand 1976; Patterson and Grabois 1986; Jacome and Morilla-Pastor 1990; Bassetti, Mathis et al. 1994; Gutling, Isenmann et al. 1996; Gosseries, Bruno et al. 2009).

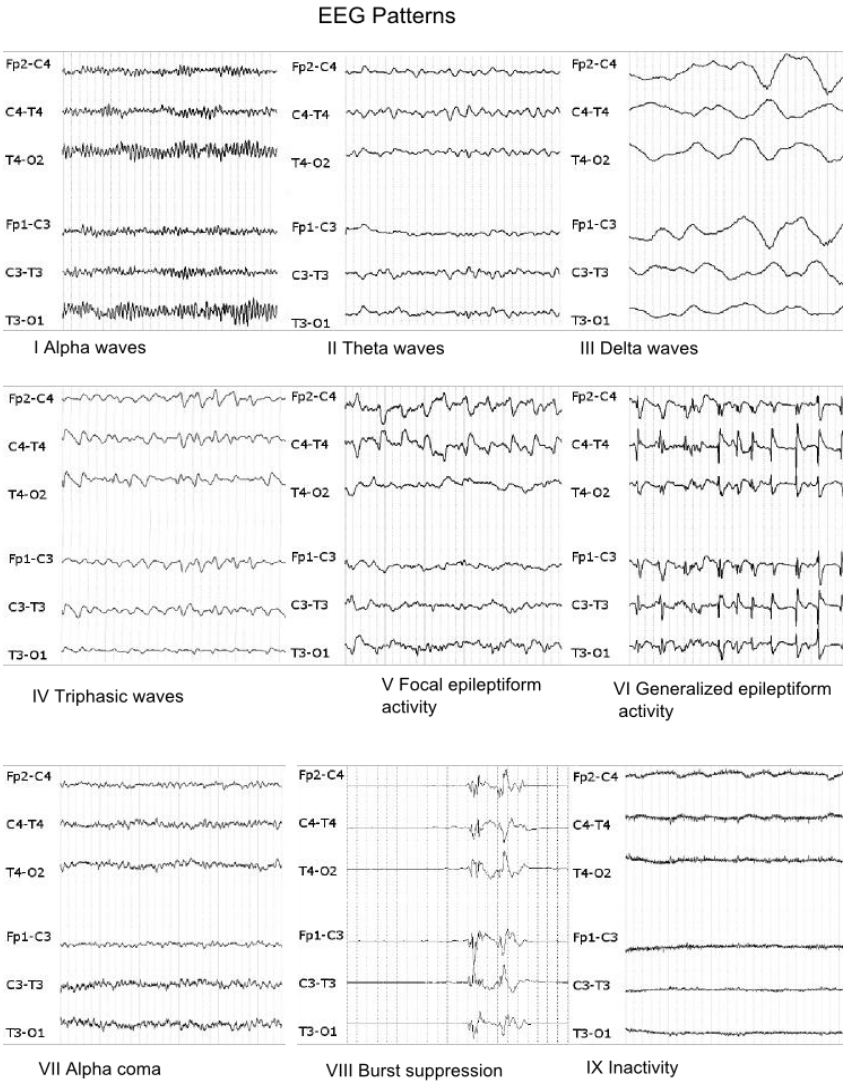


Figure 1: Nine different EEG patterns of five second duration in a "standard zero" bipolar montage with three electrodes on the right hemisphere (Fp2-C4, C4-T4 and T4-02) and three electrodes on the left hemisphere (Fp1-C3, C3-T3 and T3-01). I Alpha waves in a control patient, the eeg is symmetric and there is a posterior distribution of the alpha waves (higher amplitude at T4-02, T3-01). II. Theta waves of 4 cycles per second showing a general slowing of the brain electrical activity. III. Delta waves oscillating at one cycle per second. It can be seen in deep sleep or coma. IV. Triphasic waves, a distinctive but non-specific pattern linked to a moderate alteration of consciousness. V. Focal epileptiform activity is a sign of underlying brain lesions; here it is well seen in the fronto-central right hemisphere (Fp2-C4, C4-T4). VI. Generalized epileptiform activity. In the figure rhythmic spike waves are well visible on all electrodes. VII. Alpha coma, a pattern of bad prognosis is visible within 72 hours following the injury. It consists in diffuse irregular waves of 8-12 Hz. VIII. Burst-suppression, a pattern associated with a poor prognosis corresponds to brief periods of bursts followed by periods of electrical silence (<10uV). It often precedes cerebral death. IX. Inactivity is described as no cerebral electrical activity (<2uV). Except in cases of severe intoxication or hypothermia, it is irreversible.

Another pattern found in DOC patients is termed burst suppression, where bursts of slow waves mingled with high frequency transients are followed by periods of flat EEG (see figure

1.VIII). When the entire recording is flat or isoelectric, i.e. there is no cerebral activity of more than two micro volts; the patient can be in a state of electrocerebral inactivity (Husain 2006) (see Figure 1.IX). In this case, repeated recordings are necessary because an inactive EEG can be reversible as it is the case after drug intoxication for example. Furthermore, some VS/UWS patients can have an inactive EEG since they no longer have cortical activity while brainstem electrical activity is not detected by standard EEG recording (Brenner 2005).

Along with these abnormal patterns, the EEG recording can be very useful to detect epileptiform activity which can take different forms such as continuous generalized paroxysmal activity (figure 1.VI), paroxystic bursts, periodic lateralized epileptic discharges (figure 1.V), or focal sharp waves which can indicate epileptic discharges due to a lesion. In the case of therapeutic hypothermia after cardiac arrest, the brain activity can be followed in real time and help guide the treatment (Rossetti, Urbano et al. 2010).

The scoring of an EEG recording is subjective and therefore dependent on the investigator. To assess the severity of the state of DOC patient, Synek suggested the use of a scale consisting of five grades and including sub-grades (Synek 1988). The number of the grade increases with the severity of the injury, grade one being associated with regular alpha and some theta, while grade two has a predominant theta that may be either reactive or non-reactive. Grade three includes predominant delta and/or spindles reactive or non reactive. Grade four is reached when there is either burst suppression activity or alpha/theta coma or low amplitude activity (<20 μV). Finally grade five corresponds to electro-cerebral silence (<2 μV). Another scale was introduced by Young and colleagues to improve inter-observer agreement (Young, McLachlan et al. 1997). Furthermore, nomenclatures have been proposed to formalize the reading of an EEG trace (Hirsch, Brenner et al. 2005).

Establishing a diagnostic solely based on a single standard EEG is difficult since the patterns are not specific of the etiology and the same subject can have varying patterns in short intervals. A study based on patients in persistent VS/UWS concluded that there was no possible diagnostic use of EEG (Kulkarni, Lin et al. 2007) due to its heterogeneous and varying aspect. It can still be used to confirm the diagnosis of brain death and can still be of diagnostic importance in some cases of complete LIS patients.

Despite the limited diagnostic role of standard EEG recording, a prognosis is possible but challenging as one specific pattern can be found in encephalopathy of different origins. Furthermore, the outcome does not depend uniquely on the brain affection itself but on the overall condition of the patient. EEG information needs therefore to be backed up by etiology in order to have insights on the prognosis. For example, in the case of cardiac arrest coma, reactivity is an important feature for good prognosis; indeed a recent study showed that in the case of cardiac arrest, 10 out of 11 patients with reactivity evolved positively while only one out of 18 patients that presented a non reactive EEG had a good outcome (Thenayan, Savard et al. 2010). General scales such as the Synek scale also gave a significant correlation with the variation of the level of cognitive function between admission and after 3 months in traumatic and non-traumatic patients (Bagnato, Boccagni et al. 2010). In the case of coma due to cardiac arrest, burst suppression patterns are of bad prognosis (Niedermeyer and Da Silva 2005).

There has been much debate on the prognosis value of alpha or theta coma. It was found that unreactive alpha or theta coma is of bad prognosis but a reactive alpha or theta coma can be associated with a better outcome (Berkhoff, Donati et al. 2000). EEG variation carries a

better prognosis then an unvaried EEG, and the presence of sleep patterns in night recordings of patients are of better prognosis then if absent (Valente, Placidi et al. 2002). Furthermore, recent unpublished data including 5 VS/UWS and 6 MCS show that only MCS patients have sleep patterns, more precisely rapid eye movement sleep and slow waves cycles while the VS/UWS patients did not. Sleep patterns could therefore be used as a diagnostic tool.

3. Quantitative EEG

Standard EEG scores can be different from one reader to another. Furthermore not all the information contained in the EEG can be unveiled by visual inspection of the EEG traces and only qualitative information can be retrieved.

With the advent of digital EEG technology, the computation of complex parameters has been made possible hence providing objective measures leading to a quantitative analysis of the EEG (qEEG). For instance, one can compute the power spectral density (i.e. the distribution of the power of a signal in the frequency domain) at each electrodes thus giving local power at each frequency. The level of consciousness of a patient can be monitored with measures of signal complexity such as entropy. Levels of connectivity between electrodes can be assessed with measures of synchronization, coherence or mutual information (Nunez, Srinivasan et al. 1997; Nunez, Silberstein et al. 1999). Furthermore, using an inverse model, one can project the information at the sensor level to a source level and hence localize specific activity in the brain such as epileptic focus.

To quantitatively analyze an EEG trace, a preprocessing step is required. The EEG must be band passed to remove slow direct current drifts due to gel drying and to remove high frequencies such as muscle artifacts and line noise. Then, segments containing artifacts such as eye blinks or other movements are marked for removal. Artifacts removal can be automated using Independent Component Analysis (ICA) which decomposes the signal into independent components (Comon 1994). A component containing eye blinks or muscle tone can be removed and the signal rebuilt from the remaining components. The advantage of using ICA is that segments that would have otherwise been discarded can be used for further analysis, but the drawback is that it is unknown whether if neural information is lost in the process. Once artifact free segments of one or more seconds have been extracted, power or connectivity is computed on each segment and mean as well as standard deviation values are obtained. Statistical analysis can then be performed allowing the diagnosis and prognosis of groups of patients. For an overview of qEEG, see Tong and Takhor (Tong and Thakor 2009).

The power spectral density can be computed with the fast Fourier transform or with a wavelet transform computed on the extracted segments (Tong and Thakor 2009). It can be expressed in absolute power (uV^2) or in relative power (%) for each individual electrode or on a selected number of electrodes of a region of interest. In patients with DOC, power in higher bands such as alpha and beta decreases while power in lower bands such as delta and theta increases in relationship with the severity of the disorder (León-Carrión, Martin-Rodriguez et al. 2008); (Lehembre, Bruno et al. in press 2011).

Measures of signal complexity such as the bispectral index (BIS, Aspect Medical Systems, Newton, USA) were initially developed for anesthesia monitoring (Johansen and Sebel 2000; Rosow and Manberg 2001) but can be used to evaluate consciousness levels in DOC patients. The BIS, a unit less measure ranging from 0 (isoelectric EEG) to 100 (normal activity) derives from a combination of temporal, frequency parameters and bispectral measures. It can be seen as a black box which parameters have been empirically set and optimized on a large database of EEG recordings during anesthesia (Rampil 1998). In sleep, BIS values gradually

decrease (Noirhomme, Boly et al. 2009). In DOC patients, one study found correlations between BIS values and scores of the Glasgow Coma Scale (Gill, Green et al. 2003). However, although statistically significant, these correlations were highly variable and thus difficult to use as a diagnostic tool. Another study showed that at the group level, VS/UWS patients have significantly lower BIS than MCS patients although BIS values do not allow the diagnosis of patients at the individual level (Schnakers, Ledoux et al. 2008), still measures of BIS have a prognosis value as patients with a higher BIS recovered better. Other flexible methods based on entropy have been designed in order to synthesize the EEG information into one number. The Datex-Ohmeda S/5 entropy monitoring (GE Healthcare, Helsinki, Finland) for instance implements a time-frequency balanced spectral entropy which gives an information on the complexity of the EEG. A recent study showed a 48% reduction of the entropy in VS/UWS patients compared to controls while in MCS patients it was only reduced by 18% (Gosseries, Schnakers et al. 2011). More importantly, entropy could discriminate VS/UWS and MCS patients with a specificity and sensitivity of 90% in the acute setting, it is therefore a candidate tool for diagnosis. Furthermore this study corroborates the idea that VS/UWS have a decrease of neural network complexity, as suggested by results presented with yet another entropy measurement, the approximate entropy (ApEn) (Sarà and Pistoia 2010). ApEn also showed prognostic capabilities in a group of VS/UWS patients, low values were associated with bad outcome while higher values led to MCS, partial or total recovery. Moreover, testing of ApEn under three conditions, eyes closed, auditory and painful stimuli, yielded similar results, and could quantify the degree of complexity suppression as a function of loss of consciousness (Wu, Cai et al. 2010).

The EEG can also quantify connectivity between brain regions (Pereda, Quiroga et al. 2005). Connectivity is disrupted in patients suffering from DOC (Laureys 2005), it provides complimentary information of diagnostic and prognostic importance (Thatcher, Cantor et al. 1991). Coupling parameters between electrodes provide a connectivity measure between underlying regions. A broad array of methods can be used to assess this coupling, correlation in the time domain, coherence which is a linear correlation between two signals as a measure of frequency, or non linear methods such as mutual information. Such measures require careful interpretation as they are entailed to two inherent problems of the EEG, the reference problem and the volume conduction problem. Indeed, a single reference adds a common component to all the signals of all electrodes which will subsequently appear coupled. To address this problem, bipolar montages are used which provide reference free electrodes with the drawback of reducing the number of available electrodes. Volume conduction also adds artificial coupling between electrodes. Indeed, electrical currents produced by neural assemblies diffuse through the cerebrospinal fluid and the bone and are measured by different electrodes simultaneously, giving rise to correlated electric signals. Hence, correlation and coherence measures are affected by these biases which will typically result in high values of connectivity in neighboring electrodes. Still, coherence is well-known, and easy to use, it is therefore the most used method to assess connectivity in clinical settings. A case study on a VS/UWS patient with severe asymmetric brain damage revealed a drop of coherence in the damaged hemisphere (Davey, Victor et al. 2000). A decrease in coherence has also been observed in MCS patients (Schiff, Giacino et al. 2007). Advanced connectivity methods aiming to answer the volume conduction problem and offering more information such as the directionality of the connection have been proposed such as the imaginary part of coherency (Nolte, Bai et al. 2004), the phase lag index (Stam, Nolte et al. 2007) or granger causality (Pereda, Quiroga et al. 2005). A preliminary study using the phase lag index and the imaginary part of coherency showed that MCS patients had stronger connections in theta and

alpha band than VS/UWS patients at the group level (Lehembre, Bruno et al. in press 2011). Likewise, granger causality showed that patients in severe neurocognitive disorders (SND), an upper boundary of MCS significantly displayed more connections than MCS patients. Furthermore, a classifier based on the number of connections computed with granger causality achieved a 100% accurate classification into MCS and SND class of the 16 (7 MCS, 9 SND) patients included in the study (Pollonini, Pophale et al. 2010).

Finally, in qEEG can also be included approaches that allow the reconstitution of cerebral activity using source reconstruction methods (Michel, Murray et al. 2004). These methods are based on models of ranging complexity, from spherical brain models to realistic models based on magnetic resonance images. All parameters computed at the electrode level can also be computed at the source level, resulting in a better spatial resolution and providing a 3D visualization of the activity of the brain. Source reconstruction techniques require however a minimum of 32 electrodes, and 64 or more being recommended (Michel, Murray et al. 2004). A prospective study including 50 VS/UWS patients showed correlations between the level of recovery at three months and the power of occipital sources in the alpha range (Babiloni, Sarà et al. 2009). Recovery level, either MCS or complete recovery of consciousness could also be differentiated.

4. Event related potentials

Since the electroencephalography (EEG) cannot quantify small changes induced by sensory, motor or cognitive activities, more subtle functional variations can be investigated by averaging the EEG activity, according to the onset of a repeated stimulus. Averaging increases the signal to noise ratio therefore revealing activity that is time-locked to the stimulus while other non-stimulus related activity is averaged out. Event Related Potentials (ERP) reflects therefore the time course of information processing from low-level peripheral receptive structures to high-order associative cortices. ERPs are frequently used in clinical routine and can be classified in two categories : short latency or exogenous components, and cognitive or endogenous components (Luck 2005).

Short-Latency ERPs

Short-latency ERPs or exogenous ERPs are elicited within a time range between 0 and 100 ms after the presentation of a stimulus. They correspond to the activation of the ascending pathways to the primary cortex and are affected by the physical properties of the stimulus. The absence of exogenous components is a marker of poor outcome (Laureys, Perrin et al. 2005), most patients who do not present these components bilaterally die or end their life in a vegetative state. The presence of short-latency ERP is however not sufficient to be a good predictor of recovery since well-preserved potentials are recorded in patient who never recover.
Brainstem auditory evoked potentials (BAEP) are most often used with sounds ("clicks") using headphone. They are evoked in the first 10 ms revealing the activity from the auditory nerve to the inferior colliculus (Picton, Hillyard et al. 1974). The absence of BAEPs is also a reliable marker of bad outcome when there is no evidence of peripheral auditory injury. However, the presence of normal BAEPs does not indicate a good outcome (Fischer, Ibanez et al. 1988; Garcia-Larrea, Artru et al. 1992; Guerit, de et al. 1993; Fischer, Luaute et al. 2001).

Somatosensory evoked potentials (SEP) are elicited by sensory electrical stimulation of the median nerve at the wrists. Bilateral absence of SEPs in coma patients is strongly related with

unfavourable outcome (i.e. death or VS/UWS) especially in patients with hypoxia–ischemia etiology (Cant, Hume et al. 1986; Lew, Dikmen et al. 2003; Logi, Fischer et al. 2003; Robinson, Micklesen et al. 2003). For a large scale review including 2891 patients (Robinson and Micklesen 2004). All patients with good outcome have developed normal SEPs but they are also present in patients with unfavorable outcome (Cant, Hume et al. 1986; De Giorgio, Rabinowicz et al. 1993; Carter and Butt 2001; Amantini, Grippo et al. 2005). Likewise, middle-latency auditory-evoked potentials (MLAEPs) appearing between 10 and 50 ms and possibly related to the activation of primary auditory cortex and thalamus is strongly associated, when absent, with poor outcome in post-anoxic coma (Fischer, Luaute et al. 2006). Finally, visual evoked potentials, elicited using flashing LEDs, are less used at the intensive care because these are not systematically present even in healthy subjects (Vanhaudenhuyse, Laureys et al. 2008).

Cognitive ERPs

Cognitive ERPs or endogenous ERPs are obtained after 100 ms of the presentation of a stimulus and reflect the activity of both cortical and subcortical structures, including associative areas (Vanhaudenhuyse, Laureys et al. 2008). They depend on the psychological significance of the stimulus and are linked to the level of arousal or attention but also to the experimental condition. Using passive paradigms, cognitive ERPs assess residual cognitive functions and with active paradigms, they can be used to detect sign of consciousness in severe brain injured patients (see Table 1). Moreover, ERPs generally appear to be good predictors of favorable outcome (Daltrozzo, Wioland et al. 2007). Five cognitive components have been measured in DOC patients: the N1 component in response to a stimulus, the mismatch negativity and the P3 in response to novelty, and the N400 and P600 components in response to a semantic change.

Passive paradigms

The N1 component is a negative inflection that appears around 100 ms in response to any auditory stimulus (Hillyard, Hink et al. 1973), showing an activation of the auditory cortex (Naatanen and Picton 1987). The presence of a N1 in comatose patients indicates that the primary auditory cortex is functionally preserved. Some studies suggest that the presence of the N1 component is a good marker of recovery (Fischer, Luaute et al. 2001; Lew, Dikmen et al. 2003; Fischer, Luaute et al. 2004) whereas others suggest that its absence does not appears to be a predictor of bad outcome (Glass, Sazbon et al. 1998; Guerit, Verougstraete et al. 1999).

The mismatch negativity (MMN) is another negative component that appears around 100-250 ms after any auditory change in a monotonous sequence of sounds (i.e., an oddball paradigm) (Naatanen, Lehtokoski et al. 1997), involving the primary auditory and prefrontal cortices (Alho 1995). Its low amplitude implies that many repetitions are needed to observe a response. As subjects do not need to be attentive to the sound to detect a MMN, it indicates an automatic response generated by a comparison process between the afferent input and a memory trace developed by the repetitive stimulation. MMN is however not present in every healthy subjects. As most of healthy subjects, a few patients with DOC are likely to process sound deviance, mainly when their state is not due to anoxia. Many studies showed a high prognostic value for recovery, all etiology confounded (Kane, Curry et al. 1996; Fischer, Luaute et al. 2001; Fischer, Luaute et al. 2004; Kotchoubey 2005; Naccache, Puybasset et al. 2005; Fischer, Luaute et al. 2006). Using the subject's own name, another study also showed

a prognostic values of the MMN in recovery of consciousness from coma and VS/UWS patients (i.e., 4 of the 5 patients showing a MMN response recovered to MCS 3 months later, the other 5 patients without MMN response failed to show any clinical improvement) (Qin, Di et al. 2008). Comparing VS/UWS to MCS patients, Kotchoubey et al. reported a MMN in 65% and 34% of them respectively, with complex tones eliciting a MMN more frequently than pure tones (Kotchoubey, Lang et al. 2005). In 10 VS/UWS patients, MMN amplitude has been shown to be increased with recovery of consciousness, when patients switched to MCS (Wijnen, van Boxtel et al. 2007). However, MMN cannot be used to differentiate between VS/UWS and MCS patients (Kotchoubey, Lang et al. 2005; Fischer, Luaute et al. 2010).

The P3 is a positive component generated when subjects detect a rare and unexpected stimulus in a regular train of standard stimuli (i.e., oddball paradigm) (Sutton, Braren et al. 1965). MMN and P3 are two different brain responses generated by similar stimuli (deviant or novel) but they differ by their latency after a stimulus. For a visual potential, P3 appears around 300 ms after the presentation of the stimulus and for an auditory potential it may appear after 500 or 600 ms. The P3 corresponds to the activation of a fronto-parietal network (Pegado, Bekinschtein et al. 2010). Note again that as the MMN, not all healthy subjects present a P3. Even if simple sounds can generate a P3 or a MMN, they can also be produced by more complex stimuli with emotional valence that influence the amplitude of the evoked potential (Kotchoubey and Lang 2001; Mazzini, Zaccala et al. 2001; Lew, Dikmen et al. 2003) leading to a larger number of post comatose patients exhibiting P3 response (Marosi, Prevec et al. 1993; Signorino, D'Acunto et al. 1997). For example, the patient's own name, which is a salient attention-grabbing stimulus, is more likely to generate a P3 than a simple sound ("click") (Perrin, Schnakers et al. 2006; Schnakers, Perrin et al. 2008). As the MMN, in passive paradigms, P3 component does not allow to distinguish between VS/UWS and MCS patients (Kotchoubey 2005; Perrin, Schnakers et al. 2006; Vanhaudenhuyse, Laureys et al. 2008; Fischer, Luaute et al. 2010). Indeed, delayed P3 responses have been observed following an own name stimulus in both VS/UWS and MCS patients, suggesting partially preserved semantic processing in non-communicative brain-damaged patients (Perrin, Schnakers et al. 2006). The presence of P3 in patients with impaired consciousness in the acute stage seems also related to a good prognosis (Yingling, Hosobuchi et al. 1990; Gott, Rabinovicz et al. 1991; Glass, Sazbon et al. 1998; Guerit, Verougstraete et al. 1999; Lew, Dikmen et al. 2003; Fischer, Dailler et al. 2008). Similarly to the MMN component, the presence of a P3 component has also been found to correlate with recovery of consciousness in 34 post-traumatic VS/UWS patients (Cavinato, Freo et al. 2009).

The last component is the N400 which is a negative potential appearing about 400 ms after the presentation of a word. Its amplitude is increased if the stimulus is discordant (phonological or semantic mismatch) with respect to the context (word or sentence) (Kutas and Hillyard 1980). Semantic incongruence can also lead to a P600 which is a positive inflection 600 ms after the stimulus. Any positive or negative change can therefore be considered in the treatment of incongruence. Medial and lateral temporal cortex, as well as the left frontal and parietal cortex seem to contribute to N400 response (Smith, Stapleton et al. 1986; Hagoort, Brown et al. 1996). These inflections were observed in inattentive healthy subjects suggesting that like the MMN and the P3, N400 and P600 are also the result of an automatic process (Perrin, Garci et al. 2003; Vanhaudenhuyse, Laureys et al. 2008). A N400 response to incongruous words has been reported in some VS/UWS and in a majority of MCS patients suggesting that semantic processes can be relatively preserved in DOC patients (Schoenle and Witzke 2004). Similarly, recognition of affective prosody has been observed in

6 of 27 VS/UWS and MCS patients as well as in three LIS patients (Kotchoubey, Kaiser et al. 2009), suggesting residual detection of affective mismatch due to violations of emotional context of stimulation in DOC patients.

Active paradigms

While passive paradigms help to detect residual brain activity in severely brain injured patients, the use of new active paradigms (i.e. tasks requiring patient's participation instead of passive listening) can help to determine if the patient is conscious or not (see Table 1). If the patient is conscious, EEG signal can be used to assess the possibility of a functional communication through brain computer interfaces (BCI) (Kübler 2009; Millan, Rupp et al. 2010). The recent case of a 21-year old comatose woman who failed to show any motor sign of consciousness after 49 days following a basilar artery thrombosis (Schnakers, Perrin et al. 2009) illustrates the practical utility of demonstrating voluntary brain activity in non-clinical means. Only EEG evoked-potential based on command following (i.e., counting her own name in a list of names) permitted to make the diagnosis of *complete* locked-in syndrome (characterized by tetraplegia, anarthria and paralysis of eye motility). Indeed, in the active condition, when asking to count her own name, the P3 response observed was larger than while passively listening. This active own name paradigm using P3 was also employed on a larger number of DOC patients. Schnakers et al. studied 22 severely brain injured patients which were instructed to count the number of times they heard their own name. Some MCS patients, including patients only showing visual tracking without behavioral command following, showed an increase of the P3 responses when counting their own name compared to when listening to the names passively, documenting again command following based on brain activity only. VS/UWS patients did not demonstrate such responses (Schnakers, Perrin et al. 2008). Similarly, EEG-based evidence of conscious processing (i.e., count a deviant sound sequence in a series of beeps) was demonstrated in 3 out of 4 MCS patients while no voluntary modulation of evoked potentials was observed in 4 VS/UWS patients (Bekinschtein, Dehaene et al. 2009).

Table 1: Event related potentials studies in patients with disorders of consciousness

	References	Etiology	Interval	N	Diagnostic	Main findings
Passive paradigm						
N1	Glass et al. 1998	TBI	< 3 m	8	VS/UWS	N1 in 87% of VS/UWS with longer latency. No prognostic value for recovery.
	Guérit et al. 1999	TBI/NTBI	< 6 m	103	comatose (GCS ≤ 10)	N1 occurrence, latency and amplitude related with GCS. Presence of N1 is good prognosis but no prognostic value if absence of N1.
	Lew et al. 2003	TBI	< 1 w	22	comatose (GCS ≤ 8)	Prognostic value: N1 associated with favorable outcome.
	Fischer et al. 2004	TBI/NTBI	< 3 m	346	comatose (awake vs unawake)	Presence of N1 gives a probability of awakening up to 87%.
MMN	Kane et al. 1996	TBI	< 1 m	54	comatose (GCS ≤ 8)	Very good predictor of recovery. Presence of MMN predicted return of consciousness and preceded changes in GCS.
	Kotchoubey et al. 2003	TBI/NTBI	na	79	VS/UWS, MCS, EMCS	MMN in 65% of VS/UWS and 34% of MCS. Complex (musical) tones elicit MMN more frequently and of a larger amplitude than pure tones.
	Fischer et al. 2004	TBI/NTBI	< 2 m	346	comatose (awake vs unawake)	Prognostic value for recovery. When MMN present, 89% of patients awakened. No patient with MMN became permanently VS/UWS.
	Kotchoubey et al. 2005	TBI/NTBI	1 - 127 m	98	VS/UWS, MCS, EMCS	Presence of MMN related to a better outcome. No difference between VS/UWS and MCS.
	Naccache et al. 2005		< 3 m	30	comatose (GCS ≤ 8)	Good predictor of awakening: MMN predicted awakening with a specificity of 93%, a sensitivity of 56%, and with a positive predictive value of 90%.
	Fischer et al. 2006	NTBI	< 2 w	62	comatose (GCS ≤ 8)	Prognostic value with very high probability awakening when MMN present and nonawakening when MMN are absent.
	Wijnen et al. 2007	TBI/NTBI	< 5 m	10	VS/UWS	MMN-amplitude and latency predicted the patients' outcome on recovery to consciousness.
	Qin et al. 2008	TBI/NTBI	< 6 m	12	coma, VS/UWS, MCS	Presence of MMN correlated with recovery of consciousness. Subject's own name is effective in evoking. MMN and has potential prognostic values in predicting recovery of consciousness.
	Fischer et al. 2010	TBI/NTBI	4 - 261 m	27	VS/UWS, MCS	Presence of MMN 19%. No difference between VS/UWS and MCS.
P3	Yingling et al. 1990	TBI/NTBI	< 1 m	8	comatose (GCS ≤ 10)	Presence of P3 is related to a good prognosis in the acute stage.
	Gott et al. 1991	NTBI	< 1m	20	coma	Presence of P3 (30%) associated with awakening (83%), but absence of a P3 did not preclude it. Presence of a P3 correlated with higher GCS.
	Signorino et al.	TBI	< 1 w	25	comatose	Prediction of outcome.

	1997				(GCS ≤ 9)	Emotional stimulations increase number of responders (36% to 52%). No P3 in 40% with 50% of them died.
	Glass et al. 1998	TBI	< 3 m	8	VS/UWS	Presence of P3 is compatible with a higher probability for improvement but nondetection does not indicat bad prognosis. Presence of P3 in 38% with 67% regained consciousness (vs none of the non-responders).
	Guérit et al. 1999	TBI/NTBI	< 6 m	103	comatose (GCS ≤ 10)	Occurrence, latencies and amplitudes related with the GCS. Presence of P3 is good prognosis but no prognostic value if absence of P3.
	Lew et al 2003	TBI	< 1 w	22	comatose (GCS ≤ 8)	Presence of P3 can predict a return of consciousness. P3 associated with good clinical outcomes.
	Kotchoubey 2005	TBI/NTBI	1-127 m	98	VS/UWS, MCS, EMCS	No difference between VS/UWS and MCS.
	Perrin et al. 2006	TBI/NTBI	2 w - 10 m	15	VS/UWS, MCS, LIS	No difference between VS/UWS and MCS. Patient's own name more likely to generate a P3 than a simple sound. P3 observed in all LIS and MCS and in 3 of 5 VS/UWS. Delayed P3 latency for MCS and VS/UWS patients. Partial preservation of semantic processing in DOC patients.
	Fischer et al. 2008	TBI/NTBI	< 3 m	50	comatose (GCS ≤ 8)	Presence of P3 (42%) highly correlated with awakening. P3 increases prognostic value of MMN alone.
	Cavinato et al. 2009	TBI	2 - 3 m	34	VS/UWS	P3 correlated with recovery of consciousness. P3 highly predictive of recovery of consciousness.
	Fischer et al. 2010	TBI/NTBI	4 - 261 m	27	VS/UWS, MCS	No difference between VS/UWS and MCS. P3 in 26%.
N400	Schoenle and Witzke 2004	TBI/NTBI	na	120	VS, MCS, EMCS	Presence of N400 in some VS and in a majority of (E)MCS. Semantic processes can be relatively preserved in DOC.
	Kotchoubey et al. 2009	TBI/NTBI	2 - 108 m	30	VS/UWS, MCS, LIS	Recognition of affective prosody in 22%. Residual detection of affective mismatch due to violations of emotional context of stimulation in DOC.
Active paradigm						
P3	Schnakers et al. 2008	TBI/NTBI	1 - 288 m	22	VS/UWS, MCS	Increase of the P3 in some MCS patients in active compared to passive condition. No difference in VS/UWS.
	Schnakers et al. 2009	NTBI	1 m	1	LIS	Increase of the P3 in active compared to passive condition.
P3&MMN	Bekinschtein et al., 2009	TBI/NTBI	1 w - 6 m	8	VS/UWS, MCS	3 out of 4 MCS presented a global effect and only a local effect was observed in VS/UWS. Evidence of conscious processing.

Note. MMN = mismatch negativity; N= Number of patients; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state; EMCS = emergence of MCS; LIS = locked in syndrome; TBI=traumatic brain injury; NTBI=non traumatic brain injury; w = weeks; m = months; GCS = Glasgow Coma Scale

Another auditory BCI has been developed for a binary communication (yes/no answer) (Sellers and Donchin 2006) where users hear a sequence of four stimuli (i.e., yes, no, stop, go) presented in a random order. In order to answer a question, participants have to focus on either "yes" or "no" when hearing the sequence. A stable P3 response corresponding to the answer (yes/no) has been observed in healthy volunteers but also in ALS patients, with a lower reliability (Sellers and Donchin 2006). The first BCI study used with DOC patients was also carried out with this last paradigm in order to test its reliability as a diagnostic tool ("is the patient conscious?"). Results showed the benefits of the system to improve detection of consciousness in DOC patients. Two LIS patients were also evaluated, one showed reliable ability to use the BCI but not the other patient, suggesting that the system does not confirm the absence of consciousness in case of negative results (Noirhomme, Chatelle et al. 2010). Other auditory BCI for communication have also been proposed for ALS and locked in patients (Kübler, Furdea et al. 2009; Halder, Rea et al. 2010). A very recent paradigm, the P3-Brain Painting, has been developed to paint pictures using P3 brain activity only enabling ALS and LIS patients to express themselves creatively (Münßinger, Halder et al. 2010).

Changes in sensorimotor rhythms (SMRs) or mu rhythms have also been employed in BCIs. SMRs refer to an EEG activity of 8-15 Hz recorded in the primary sensorimotor cortex (Wolpaw, Birbaumer et al. 2002), usually accompanied by a beta activity of 18-26 Hz. This activity can be reduced or desynchronized using preparation, execution, or imagination of movement, particularly in the contralateral motor cortex. An increase in the rate (or synchronization) occurs after the execution of a movement and during relaxation (Pfurtscheller and Lopes da Silva 1999). The advantage is that these components do not require the actual execution of the movement but kinesthetic imagination is enough to make them appear (Pfurtscheller, Neuper et al. 1997). It is however only possible to integrate two commands, more commands leading to a decrease in classification accuracy. In healthy subjects, many BCIs based on SMRs have shown good results for writing words in both visual (Scherer, Muller et al. 2004) and auditory (Nijboer, Furdea et al. 2008) modality. A completely paralyzed patient was also able to use a BCI based on SMRs to communicate through a virtual keyboard with a set of letters (Birbaumer, Ghanayim et al. 1999; Neuper, Muller et al. 2003). To select a letter, the patient had to perform a mental task (i.e. movement imagery) and after several months, he was able to control the keyboard with an accuracy of 70%. The SMRs were also used recently with DOC patients showing the ability of a patient clinically diagnosed as VS/UWS to respond to the command (imagine squeezing the right hand versus imagine moving all toes) (Cruse, Bekinschtein et al. 2010).

Finally, slow cortical potentials (SCPs) are the lowest frequencies generated by the cortex that can be used for BCI. They consist in slow potential shifts lasting 300 ms to several seconds. Negative SCPs are usually associated with movement involving cortical activation, while positive SCPs are associated with a reduction in cortical activity (Birbaumer 1997). Again, this system involves only 2 commands. Subjects learn to control their brain activity through operant conditioning and are subsequently able to move an object on a screen (Elbert, Rockstroh et al. 1980). People with ALS in advanced stages have been able, after training, to use this device to write words by increasing or decreasing their brain activity to select a target letter (Kubler, Kotchoubey et al. 1999).

6. Summary

Electroencephalography encompasses a palette of different techniques helping in the assessment of consciousness in brain injured patients. We reviewed herein results obtained with four main EEG-based approaches in the prognosis and diagnosis of disorders of consciousness.

First, standard clinical EEG, recorded in patients at rest is a routine examination in neurological units. In the context of comatose patients it is limited by a low spatial resolution and has little diagnostic value. It has however a prognosis value, in the cases of alpha/theta coma, or burst suppression patterns, it is of unfavorable prognosis. When the EEG is reactive to stimulations, or has varying patterns, it is a sign of better prognosis.

A step further can be taken with qEEG which gives access to a wide spectrum of objective measurements of cerebral activity providing information on the state of consciousness of a patient. Encouraging results have shown differences between groups of patients at the diagnostic and prognostic level. It is however not possible at this date to identify a parameter providing a correct diagnosis at the individual level. Future challenges will consist in linking the unmet temporal resolution of the EEG to the spatial resolution of the fMRI in order to have a better understanding of the state of consciousness of patients.

A third approach coined event related potentials is based on the averaging of stimulus time locked events, hence improving the signal to noise ratio of the EEG. There are two categories of ERPs, firstly, short latency ERPs or exogenous components are elicited by external stimulations. When absent, these ERPs are associated with bad outcome, although if present they are not necessarily related to recovery. Second, endogenous components or cognitive ERPs aim to assess cognitive residual functions (in passive paradigms) and consciousness (in active paradigms). The different components reviewed here, the N1, MMN, P3, N400 and P600 are all markers of good prognosis but can be present in both VS/UWS and MCS patients. They therefore cannot be used to establish a diagnosis in a passive paradigm. This can be achieved with active paradigms, where the patient is asked to focus on one task (for example counting the number of occurrences of own names). Indeed the amplitude of the components is different in passive and active paradigms hence providing a marker of consciousness.

Once that signs of consciousness have been observed in a patient, EEG based brain computer interface could prove useful in providing a mean of communication for patients in minimally conscious states. Brain computer interfaces are in constant evolution and transfer bit rates as high as 50 bit/min have been reported. Preliminary studies in DOC underlined the challenges of these patients as one LIS patient could use the BCI while another could not. Furthermore, visual BCIs have to be adapted as comatose patients often have impaired eye movements or reduced visual acuity. The same goes for auditory BCIs as some patient have damaged auditory pathways. Providing a direct communication pathway from the brain in comatose patient requires therefore a case by case adaptation and future research should aim to identify for each individual the BCI design that will allow the best performances.

7. References

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Abnormal corticospinal excitability in patients with disorders of consciousness

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Abstract

Background: Transcranial magnetic stimulation (TMS) has been frequently used to explore changes in the human motor cortex in different conditions, while the extent of motor cortex reorganization in patients in vegetative (VS) (now known as unresponsive wakefulness syndrome, UWS) and minimally conscious (MCS) states due to severe brain damage remains largely unknown.
Objective/hypothesis: It is hypothesized that cortical motor excitability might reveal changes as a function of consciousness impairment in patients with disorders of consciousness.
Methods: Corticospinal excitability was assessed in 47 patients (24 VS/UWS and 23 MCS) and 14 healthy controls. The test parameters included maximal peak-to-peak M-wave (Mmax), F-wave persistence, peripheral and central motor conduction times, sensory and motor evoked potential latencies, resting motor threshold (RMT), stimulus/response curves, and short latency afferent inhibition (SAI). TMS measurements were correlated to the level of consciousness (assessed using the Coma Recovery Scale-Revised).
Results: On average, the patient group had lower Mmax, lower MEP amplitude, higher RMTs, narrower stimulus/response curves, and reduced SAI compared to the healthy controls ($p < 0.05$). The SAI alterations were correlated to the level of consciousness ($p < 0.05$).
Conclusions: The findings suggest that consciousness recovery might be linked to the normalization of cortical excitability parameters as there is a significant relationship between cortical inhibition and clinical consciousness dysfunction.

Keywords

Vegetative state; unresponsive wakefulness syndrome; minimally conscious state; brain injury; transcranial magnetic stimulation; motor evoked potentials; short latency afferent inhibition.

Introduction

Following severe brain damage, disorders of consciousness (DOC), such as vegetative (VS) (now known as unresponsive wakefulness syndrome, UWS) (1) or minimally conscious state (MCS) have been linked to poor long term prognosis (2). The recovery of consciousness could be related to the number of surviving neurons and the functional integrity of long-range cortico-cortical and cortico-thalamo-cortical connections (3). Transcranial magnetic stimulation (TMS) is an objective method to assess the motor cortex excitability and the integrity of motor pathways (4). Several studies indicate that cortical injuries, independent of their etiology, can lead to a reduced strength of inhibitory neurotransmission (5-8). Paired TMS has been used for over 20 years to investigate recovery of motor function in stroke patients (for review see 9). Cortical excitability is also shown to correlate with the severity of brain damage in patients with diffuse traumatic brain injury (TBI) (10-14) and to be related to the clinical recovery in mild to moderate TBI (15). By coupling peripheral nerve stimulation with TMS, it is possible to modify the excitability of the motor cortex (16). This effect, named short-latency afferent inhibition (SAI), is produced by inhibitory interactions within the cerebral cortex (17). SAI is reduced in cholinergic forms of dementia, while it is normal in non-cholinergic forms of dementia (for review see 18). The amount of SAI is decreased in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and cognitive impairment (19). Changes in cortical excitability in patients with DOC due to severe cerebral damage remain largely unknown (20). To date, only one study has reported significant differences in motor threshold (MT) levels in persistently unresponsive post-comatose patients with brain injury due to anoxia and trauma (21). Therefore, this investigation was designed to evaluate the cortical motor phenomena that indicate the strength and integrity of corticospinal pathways in patients with DOC due to severe brain damage. Moreover, we wanted to assess the relationship between SAI measures in the motor cortex and the clinical measures of consciousness.

Hypothesis

It is hypothesized that cortical motor excitability might reveal changes as a function of consciousness impairment in patients with DOC.

Methods and Patients

Participants

Forty seven patients with severe brain damage (trauma, n=21; anoxic-ischemic encephalopathy, n=16; ischemic or hemorrhagic stroke, n=9; encephalitis, n=1) were prospectively included and met the criteria (22, 23) defining VS/UWS (n=23; 16 males; mean age ± SD 45 ± 22 years; mean time since injury ± SD 16 ± 53 months), or MCS (n=24; 19 males; mean age ± SD 41 ± 17 years; mean time since injury ± SD 36 ± 65 months). All patients were screened in order to ensure there were no contraindications to TMS (24). No sedative medication was administered prior to the TMS measurements. Thirteen patients received no centrally acting drugs, 21 patients received one centrally acting drug (antidepressant (n=1), anticonvulsant (n=8), benzodiazepine (n=2),

antispasticity drug (n=10)), and 13 patients received a combination of two or more of these drugs. The administration of these drugs could not be stopped for clinical reasons. Fourteen healthy volunteers (8 males; mean age ± SD 33 ± 11 years) were also tested.
The study was approved by the Ethics Committee of the Liège University and Liège University Hospital and written informed consent was obtained from the patient's legal guardians and healthy participants.

Clinical assessment
Coma Recovery Scale-Revised (CRS-R) (25) assessment was performed by an experienced neuropsychologist the day of, day before and day after the TMS sessions (the highest score was chosen for further analyses). The CRS-R consists of six subscales (auditory, visual, motor and oromotor/verbal functions, communication and arousal) and the maximum score is 23. In the current study, mean total CRS-R score ± SD was 4 ± 1 points in VS/UWS patients and 13 ± 5 points in MCS patients. Mean motor CRS-R score ± SD was 1 ± 1 points in VS/UWS patients and 3 ± 2 points in MCS patients (0 = none/flaccid; 1 = abnormal posturing; 2 = flexion withdrawal; 3 = localization to noxious stimulation; 4 = object manipulation; 5 = automatic motor response; 6 = functional object use).

Basic electromyographic recordings (EMG)
EMG was recorded using Ag-AgCl surface electrodes over the first dorsal interosseous muscle (FDI). The electrodes were placed on the metacarpophalangeal joint (reference) and over the motor point (active). The EMG was recorded with the "Cambridge 1401" amplifier (Cambridge, UK), low pass filtered at 3 kHz and high pass filtered at 10 Hz. The data were stored on a computer for off-line analysis. The maximal peak-to-peak M-wave (M-max) of the FDI was measured following electrical stimulation of the ulnar nerve (0.2 ms square-wave constant current pulse) at the wrist with the cathode placed distally. The supramaximal electrical ulnar nerve stimulation was performed to elicit a recurrent discharge from spinal motor neurons (F-wave). F-wave persistence was defined as the number of potentials with an amplitude of at least 20 μV out of 20 recordings (26). Peripheral motor conduction time (PMCT) was measured as the latency of the response from the spinal cord to the muscle, calculated using the formula (F+M-1)/2, where F was the shortest latency of 20 consecutive F-waves, M was the M-wave latency, and 1 was the delay time (in ms) for antidromic activation of the alpha motor neuron (27). Central motor conduction time (CMCT) was calculated as the difference between the cortical MEP latency and PMCT. Somatosensory evoked potentials (SEP) were registered from both hemispheres as described previously by Tokimura et al. (28). Five hundred responses were averaged to identify the latency of the N20 peak.

TMS
Both hemispheres were stimulated using TMS (200 stimulator and figure of eight shaped coil, Magstim Company Ltd, U.K.), and test responses in the contralateral FDI were recorded. In all experiments, the magnetic coil was held tangentially to the head with the handle pointing backwards and 45º laterally from the midline. The coil was placed at the cranial site from which a maximum FDI response was obtained (i.e. the 'hotspot'). The hotspot was marked directly on the scalp to ensure constant coil position during the entire experimental session. The resting threshold

intensity (RMT), expressed as a percentage of the maximum stimulator output, was defined as the intensity needed to produce a response of 50 μV (peak-to-peak) or more in at least five out of ten consecutive stimuli in the relaxed muscle (29). The RMT was assessed in both hemispheres. Stimulus/response curves (30) were measured with a stimulus intensity increasing in 10% steps from RMT to 40% above RMT. Five trials were performed for each stimulus intensity. Short latency afferent inhibition (SAI) was measured in the relaxed muscle by paired-pulse stimulation paradigm (17). Conditioning stimuli (CS) were 0.2 ms single pulses of electrical stimulation applied through bipolar electrodes to the median nerve at the wrist with the cathode positioned proximally. The intensity of the CS was slightly greater than motor threshold for abductor policis brevis muscle, and the magnetic test stimulus (TS) had an intensity of 120 % RMT. Nine interstimuli intervals (ISIs) between CS and TS were determined relative to the latency of the N20 component of the SEP: -2, 0, +2, +4, +6, +8, +10, +12, +14 ms. Each TMS block consisted of 50 randomized stimuli: five single TS and five CS+TS at each ISI; the interval between each TS was 8 seconds.

Statistical Analysis

Basic EMG parameters were analyzed with STATA (Stata version 9.2, Texas, U.S.A.) using Kruskal–Wallis and Mann-Whitney tests. Stimulus/response curves and SAI results were analyzed using a linear mixed model (SAS 9.1 procedure PROC MIXED; SAS Institute Inc., 2002-2003) with consciousness state (VS/UWS, MCS, and healthy controls) and stimulation condition (for the stimulus/response curves: from RMT to RMT +40 % in steps of 10 %; for the SAI: single TS and CS+TS with ISI of -2, 0, +2, +4, +6, +8, +10, +12, +14 ms relatively to N20) as systematic factors and subject as a random factor. The random subject factor also modeled the correlation between repeated measurements on subjects across stimuli. MEP values were log-transformed, median MEP values were summarized from five MEP trials by each stimulation condition per individual. The statistical null hypothesis of no difference between relative amplitude levels (stimulus/response curves: relative to RMT response; SAI: relative to the single TS response) was tested, and if a difference was detected, the statistical significance of each relative amplitude level was also tested. For the stimulus/response experiment, the statistical significance of the RMT was tested by adding the natural logarithm of RMT values as a continuous explanatory variable to the statistical model. Finally, for patients, the association between individual ratios of median SAI values at N20+2ms relative to the median of single TS responses and the corresponding CRS-R values was tested by the Spearman correlation coefficient. Results were considered significant at $p<0.05$.

Results

Basic electrophysiological parameters

TMS was tolerated well and no side effects were reported. Basic clinical and electrophysiological parameters are summarized in the Table 1. The Mmax differed between both VS/UWS and MCS compared to healthy subjects ($p< 0.001$), but not between VS/UWS compared to MCS ($p=0.8$). Unconditioned MEP amplitude was different between both patient groups compared to healthy subjects ($p<0.05$), and between VS/UWS compared to MCS ($p=0.02$). The RMT differed between VS/UWS compared to healthy subjects ($p=0.01$, Figure 1), but not between MCS compared to healthy subjects ($p=0.08$) or between VS/UWS compared to MCS ($p=0.5$). The decrease in MEP

amplitude was observed with increasing RMT (e.g. a doubling of RMT reduced MEP amplitude with 70%). MEP amplitude tended to be higher in patients using centrally acting drugs (mean 70% (CI [-9%; 216%]), but the effect was not significant (p=0.09)).
The MEP and SEP latency, F-wave persistence, PCMT, and CMCT did not differ between patient groups and healthy controls (p>0.05).

Variables	**Healthy**[1]	**MCS**[2]	**VS/UWS**[3]
Age (years)	32.7±10.3	40.7±17.2	45.0±22.3
Time since injury (months)	/	35.9±66.8	16.9±53.6
CRS-R total score (points)	/	13.3±4.8	4.4±1.3
CRS-R motor score (points)	/	3.4±1.6	1.2±0.7
Mmax (mV)	10±2.3	4.8±2.0*	5.1±2.9*
F-wave persistence (number)	13.5±5.1	16.1±5.8	17.4±4.4
SEP latency (ms)	19.3±1.1	20.4±1.8	20.2±2.0
MEP latency (ms)	22.3±1.2	22.5±2.2	22.8±2.4
PMCT (ms)	16.4±1.2	16.7±1.8	16.6±1.6
CMCT (ms)	5.9±1.2	6.2±2.6	6.7±3.3
RMT (% MSO)	39.3±7.6	49.1±18.9	50.9±13.3*
Unconditioned MEP paired-Pulse paradigms (mV)	7.4±607	8.8±7.5	4.35±5.9*†

Table 1: Basic clinical and electrophysiological characteristics.
Values are mean ± standard deviation. Abbreviations: MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome; M-max, maximum peak-to-peak M-wave; F-wave persistence, number of potentials with an amplitude of at least 20 μV out of 20 F-wave recordings; PMCT, peripheral motor conduction time; CMCT, central motor conduction time; SEPs, sensory evoked potentials; MEPs, motor evoked potentials; RMT, resting motor threshold; MSO, maximal stimulator output; uMEP, unconditioned MEP to the single magnetic test stimulus. [1] In healthy subjects MEPs were recorded bilaterally, the data presented are from the dominant hemisphere. [2] In one MCS patient no MEPs could be elicited from both hemispheres. In 7 patients MEPs were only elicited from one hemisphere. In 16 MCS patients MEPs were elicited bilaterally, the data presented are from the best side. [3] In four VS patients no MEPs could be elicited from both hemispheres. In 5 patients MEPs were only elicited from one hemisphere. In 14 patients MEPs were elicited bilaterally, the data presented are from the best side. *p<0.05 between VS/UWS patients and healthy controls, and MCS patients and healthy controls. † p<0.05 between VS/UWS and MCS patients.

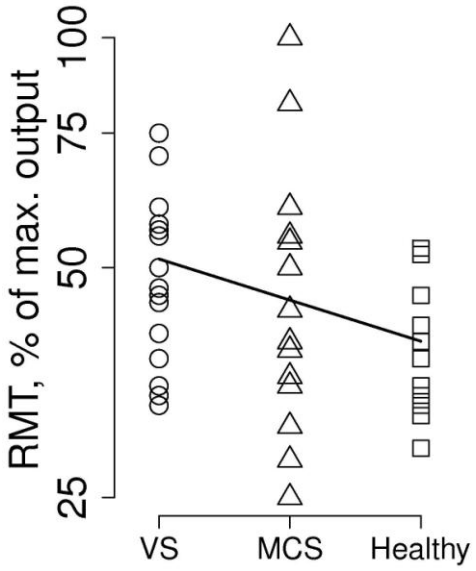


Figure 1: RMT in DOC patients and healthy controls. The RMT differed between VS/UWS (circles) compared to healthy subjects (squares), (p=0.01), but not between MCS (triangles) compared to healthy subjects (p=0.08) or between VS/UWS compared to MCS (p=0.5). The decrease of MEP amplitude was observed with increasing RMT. The fed line represents mean RMT values. Abbreviations: RMT, resting motor threshold; VS/UWS, vegetative state/unresponsive wakefulness syndrome; MCS, minimally conscious state; MEP, motor evoked potential.

Stimulus/response curves

Stimulus/response curves exhibited a gradual increase in MEP amplitude with increasing stimulus intensities. Comparisons revealed differences between the relative MEP curves for VS/UWS, MCS and healthy controls ($p<0.0001$, Figure 2). Significant differences were shown between VS/UWS and healthy controls ($p<0.005$), and between VS/UWS and MCS ($p<0.005$) for 110%, 120%, 130% and 140% of RMT intensities, while no significant differences were found between MCS and healthy controls ($p>0.05$). The model predicted that subject MEP amplitude levels were associated with RMT values ($r =-0.20$, $p=0.002$) indicating a potential effect of RMT on MEP values. High values of RMT were more likely to introduce missing MEP values by exceeding the maximal output limit (i.e. introducing a negative bias on MEP values for high RMT values). This bias was presumably larger for patients.

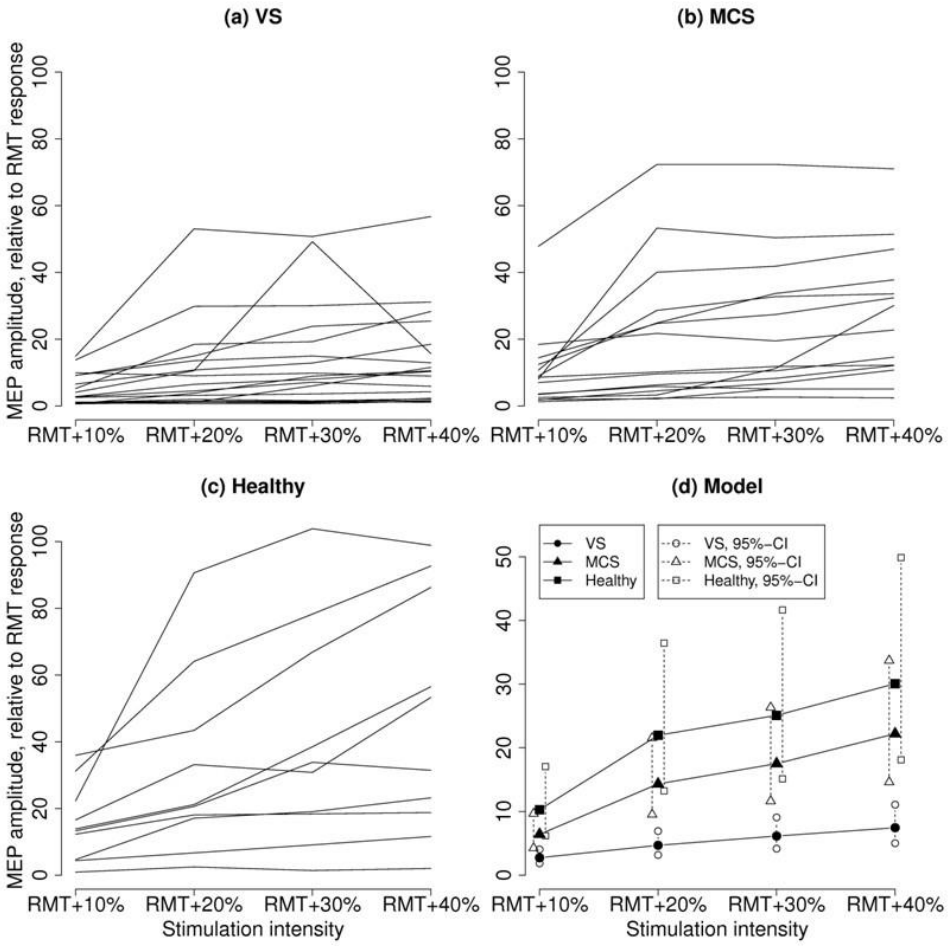


Figure 2: Stimulus/response curves in patients and healthy controls. Individual stimulus/response curves in the FDI recorded in (a) VS/UWS, (b) MCS, and (c) healthy controls. (d) Model of MEP amplitude relative to RMT response in the three groups: VS/UWS (black circles); MCS (black triangles); and healthy controls (black squares); empty symbols represent 95% confidence intervals. Stimulus intensity is expressed as a percentage of the maximum stimulator output and adjusted to RMT. Significant differences were shown between VS/UWS and healthy controls ($p<0.005$), and between VS/UWS and MCS ($p<0.005$) for 110%, 120%, 130% and 140% of RMT intensities, while no significant differences were found between MCS and healthy controls ($p>0.05$). Abbreviations: FDI, first dorsal interossei muscle; RMT, resting motor threshold; VS/UWS, vegetative state/unresponsive wakefulness syndrome; MCS, minimally conscious state; MEP, motor evoked potential.

Short Afferent Inhibition

Relative SAI time courses were different between groups ($p<0.0001$, Figure 3). The responses were inhibited in healthy controls with the most pronounced inhibition when the median nerve stimulus was given at N20+2ms before the TMS stimulus ($p=0.0000$). At this ISI interval ratios of median SAI values to the median of single TS responses were 0.31 (CI [0.2; 0.48]) in healthy controls, 0.81 (CI [0.57; 1.16]) in MCS, and 0.97 (CI [0.68; 1.4]) in VS/UWS, with a significant difference between MCS and healthy controls ($p=0.0008$, CI[1.5; 4.54]), and between VS/UWS and healthy controls ($p=0.00008$, CI [1.78; 5.44]), while the difference between VS/UWS and MCS did not

reach the significance (p=0.5, CI[0.72; 1.99]). There was no effect of centrally acting medication (p=0.7) (inter-individual variation remained 77%). As shown in Figure 4, the amount of inhibition at N20+2ms correlated with CRS-R total scores (r = - 0.39, p=0.02).

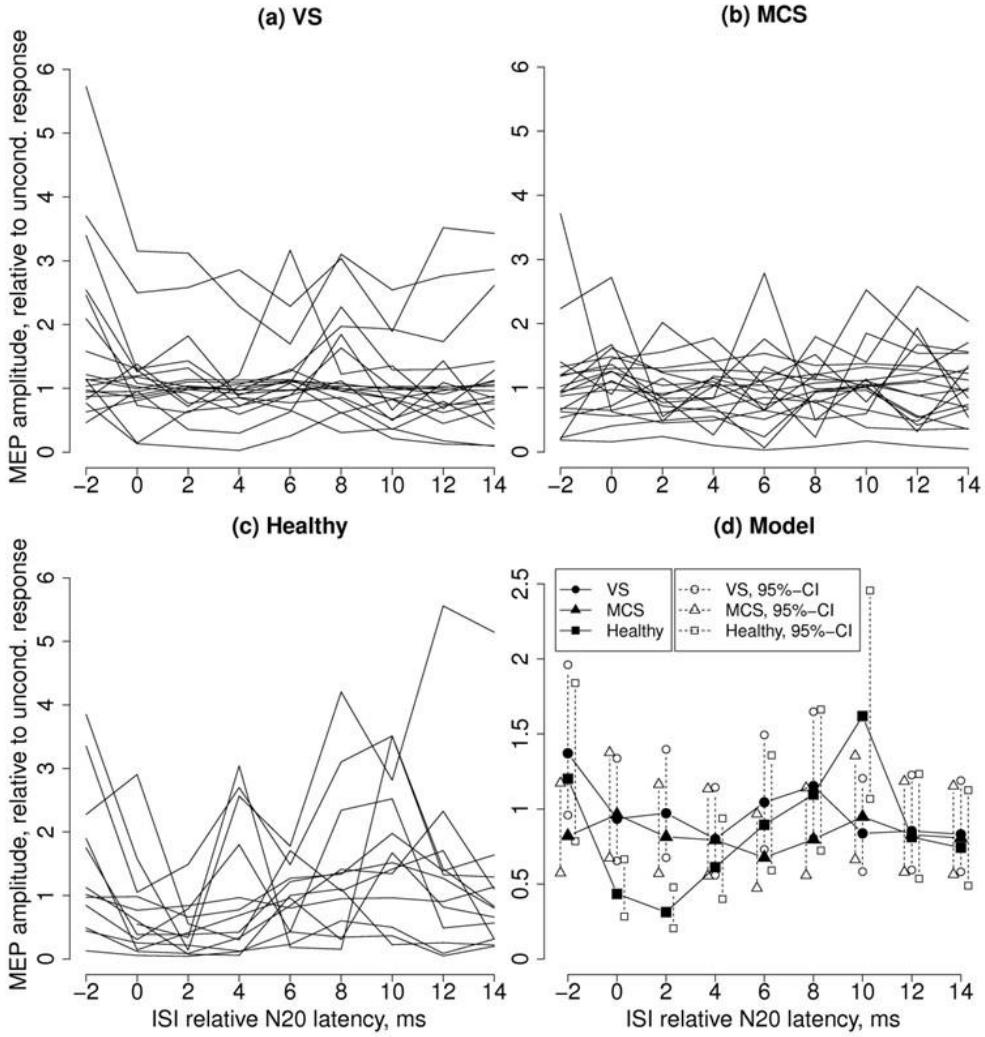


Figure 3: SAI in patients and healthy controls. Individual SAI curves in (a) VS/UWS, (b) MCS, and (c) healthy controls. (d) Model of MEP amplitude relative to unconditioned MEP response in the three groups: VS/UWS (black circles); MCS (black triangles), and healthy controls (black squares). Nineteen VS/UWS and 19 MCS patients contributed to the SAI data. The conditioning median nerve stimulation preceded TMS of the contralateral motor cortex (nine different ISI) and was adjusted for the latency of the N20 component of the SEP in each subject. The log-transformed ratios of the conditioned/unconditioned MEPs are plotted. Relative SAI time courses were different between groups (p<0.0001). *Post hoc* analysis showed a significant difference between MCS and healthy controls (p=0.0008), and between VS/UWS and healthy controls (p=0.00008), while the difference between VS/UWS and MCS patients did not reach the significance (p=0.5). Abbreviations: SAI, short latency afferent inhibition; VS/UWS, vegetative state/unresponsive wakefulness syndrome; MCS, minimally conscious state; MEP, motor evoked potential; SEP, sensory evoked potential, ISI, interstimuli interval.

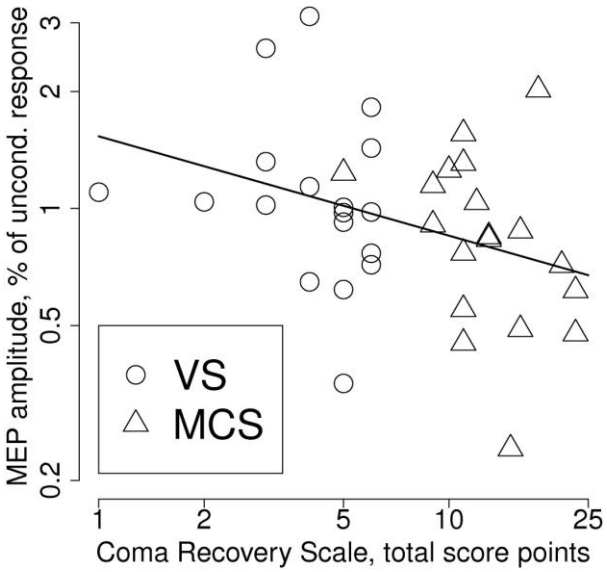


Figure 4: Correlation of SAI with clinically assessed level of consciousness. The log-transformed individual ratios of the conditioned/unconditioned MEP amplitudes at ISI+2ms (relative to N20 component of SEP) were correlated with CRS-R total scores in VS/UWS and MCS patients (r= – 0.39, p=0.02). Abbreviations: SAI, short latency afferent inhibition, MEP, motor evoked potential; SEP, sensory evoked potential; ISI, interstimuli interval; CRS-R, Coma Recovery Scale Revised (Giacino et al., 2004); VS/UWS, vegetative state/unresponsive wakefulness syndrome; MCS, minimally conscious state.

Discussion

The current study evaluated several excitatory and inhibitory phenomena in VS/UWS and MCS patients due to severe brain injury and showed that RMT, stimulus/response curves, and SAI were significantly different between patients with DOC and healthy controls. In addition, the findings revealed a relationship between SAI and clinically assessed levels of consciousness in patients with severe brain injury.

In the present study no MEPs could be elicited from both hemispheres in one MCS and four VS/UWS patients. In seven MCS and five VS/UWS patients MEPs were only elicited from one hemisphere. This is in agreement with previous studies in stroke patients, showing that presence or absence of MEPs in the weeks and months after insult does not always anticipate clinical improvement (31, 32). Both VS/UWS and MCS patients presented normal MEP and SEP latencies, F-wave persistence, PCMT, and CMCT. These results are in line with Moosavi et al. (21) showing that the absence of voluntary movements do not invariably predicate an abnormal motor conduction in post-comatose patients with severe brain damage. The previous observations made with conventional MEPs showed that motor deficit can exist in the presence of normal cortico-motoneuronal conduction times, showing that intactness of these connections is not a sufficient condition for preservation of voluntary motor activities (33). This might indicate the selective involvement of the small pyramidal tract neurons with a relative sparing of the large fast conducting corticospinal fibres that are responsible for MEP (34). In the current study, both VS/UWS and MCS

patients showed significantly lower M-max, which might indicate neuromuscular sequelae of critical illness polyneuropathy and myopathy (35). For the detection of the failure of corticospinal tract conduction, the triple stimulation technique, which consists of one transcranial magnetic and two peripheral electric stimuli (plexus and nerve) delivered along the motor pathways, might have higher sensitivity than conventional MEP or CMCT testing (36). We observed higher RMTs in VS/UWS patients compared to healthy controls, while the difference between MCS patients and healthy subjects was not significant. These results confirm previous findings of higher MT in patients recovering from anoxia (21) and diffuse TBI (14, 15). The RMT is thought to reflect membrane excitability in interneuronal circuits within the motor cortex (37). Diffusion-weighted imaging has also shown that the RMT is strongly correlated with the structural integrity of the white matter in the primary motor and premotor cortex (38). RMT is also determined by the excitability of spinal motoneurons as discharges of these are required for a MEP to be evoked in the muscle (39). However, we found the F-wave persistence to be within normal limits in both patient groups, suggesting that most of the increase in RMT was caused by reduced cortical excitability. In concurrence with these findings, a difference between VS/UWS patients and healthy controls, and between VS/UWS and MCS patients was observed in the stimulus/response curves, while no significant differences were found between MCS patients and healthy controls. Compared to RMT, stimulus/response curves assess neurons that are intrinsically less excitable and further from the centre of activation of the TMS coil (40), and are believed to reflect the size of the cortical representation and the distribution of excitability within the corticospinal projections (39).

The present study revealed a significantly reduced SAI in patients with DOC. This is in concurrence with studies demonstrating a reduced SAI in patients with diffuse TBI (10) and stroke (41). Some evidence suggests that SAI is a cortical phenomenon (28) and might be related to central cholinergic activity (42, 43). The mechanisms behind SAI abnormalities in DOC remain unclear, but could possibly involve the withdrawal of tonic facilitation from the thalamus (44). Alternatively, subcortical lesions interrupting ascending cholinergic axons may lead to cortical cholinergic denervation (45). However, it cannot be excluded that SAI occurs via cholinergic modulation of inhibitory circuits rather than direct inhibitory cholinergic effects (41-43). In this respect, investigation of short and long latency intracortical inhibition and facilitation in patients with DOC could be important. A correlation between SAI and clinically assessed levels of consciousness was observed, which is in agreement with studies showing a correlation between SAI and neuropsychological measures related to long term memory and other cognitive functions in patients with Alzheimer's disease (46) and vascular dementia with mikrobleeds (47, 48). A recent study in acute stroke patients showed a correlation between SAI and long-term recovery (41). The hypothesis that cholinergic neuronal function is impaired in brain damaged patients is also supported by preliminary pharmacological studies using acetylcholinesterase inhibitors to improve memory during acute brain injury rehabilitation (49, 50).

Some limitations should be highlighted in the current study. TMS measurements could be influenced by the centrally acting drugs administered to the patients (as standard care in the rehabilitation hospital). It has been shown that benzodiazepines can reduce SAI (51); however, the influence of other centrally acting drugs on SAI has not been thoroughly investigated. While some

information has been gathered on how individual drugs influence TMS (52), the effects of different drug combinations, often used in severely brain damaged patients, remain unclear. Despite this, in the current study, cortical excitability measures did not reveal drug-related differences. A second caveat relates to the fluctuating levels of arousal frequently encountered in DOC patients, possibly altering the recorded cortical excitability parameters. In the current study, a standardized arousal facilitation protocol as defined in the CRS-R (22) was delivered to the patients. While the continuous assessment of arousal in patients with DOC is clinically challenging, future studies could use simultaneous EEG recordings to assist in identifying sleep patterns during TMS acquisitions. Finally, in the current study here was heterogeneity in the size, location, severity, and type of focal lesions in the participants with different brain injury etiology. Future studies should correlate the amount of inhibition as measured by TMS with the structural abnormalities in the cholinergic pathways (53) and the integrity of the tissue in subcortical, thalamic and brainstem regions (54) as measured using MRI (e.g. diffusion tensor imaging, fractional anisotropy, voxel-based morphometry). Nevertheless, this study demonstrates TMS changes in patients with DOC due to severe brain injury, and supports TMS as an assessment tool to provide objective complementary information and add further information to DOC as cortico-cortical disconnection syndrome (55-57).

In conclusion, the current study is the first to provide detailed information on the integrity of the corticospinal sensorimotor pathways in patients with DOC due to severe brain damage. The higher RMTs, narrower stimulus/response curves, and reduced SAI in patients with DOC might reflect a decreased cortical excitability and a reduced cortical inhibitory activity. Moreover, reduced SAI correlated with the clinically assessed level of consciousness in patients with DOC. The hypothesis that reduced SAI is related to impaired cholinergic neuronal function in patients with DOC should be explored further in the pharmacological studies. We suggest that in severe brain damage, functional recovery of consciousness might be linked to restoration of normal corticospinal and intracortical mechanisms. Longitudinal studies in patients with DOC would allow further assessment of this hypothesis, which, if confirmed, might offer prognostic surrogate markers and suggest novel therapeutic strategies.

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TMS/EEG in severely brain-injured patients: methodological aspects

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Abstract

Background: Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) may represent a powerful tool to probe cortical excitability and connectivity in humans. However, the empirical demonstration that it is possible to record TMS-evoked EEG potentials (TEPs) that are unconfounded by extra-cerebral artifacts is missing.

Objective: to demonstrate that, by implementing the appropriate procedures, it is possible to record TEPs that purely reflect electrical responses of the cortical tissue to TMS.

Methods: TEPs were recorded by applying navigated TMS/EEG in three awake patients with a diagnosis of unresponsive wakefulness syndrome/vegetative state. Methodological procedures were applied to eliminate extra-cerebral confounding factors such as muscle artifact and auditory evoked potentials. Structural and functional imaging data showed diffuse anoxic lesions in Patient 1, widespread lesions in the left hemisphere in patient 2 and focal lesions in both hemispheres in patient 3.

Results: in all three cases, TEPs were absent when TMS was targeted on cortical lesions (as assessed by structural and functional imaging) and were present otherwise.

Conclusions: TMS/EEG technique allows to measure genuine cortical responses without extra-cerebral artifacts. TEPs were present only when preserved and functioning cortical circuits were stimulated. Assessing cortical excitability and connectivity in patients with brain injury requires accurate targeting by means of a neuronavigation system.

Introduction

The combination of single-pulse transcranial magnetic stimulation and electroencephalogram (TMS/EEG) allows one to measure, directly and non-invasively the electrical reactivity of cortical circuits (excitability) and the causal interactions among cortical areas (effective connectivity) in humans. Indeed, TMS-evoked potentials (TEPs) have been recorded to assess cortical excitability and effective connectivity and their changes during wakefulness (Ilmoniemi *et al.*, 1999; Massimini *et al.*, 2005; Rosanova *et al.*, 2009; Casali *et al.*, 2010) deep sleep (Massimini *et al.*, 2005), anesthesia (Ferrarelli *et al.*, 2010) and attention shifts (Morishima *et al.*, 2009). However, whether TEPs are genuine responses of the cerebral cortex or confounded by the activation of extra-cortical sources (scalp muscles, eye movements, auditory evoked potentials), is still an open issue. At present date, direct experimental evidence that TEPs exclusively reflect activation of the cortical tissue is still missing.

In a recent paper, we successfully recorded TEPs in severely brain-injured patients suffering from disorders of consciousness in order to monitor the possible resurgence of cortical effective connectivity in patients who recover from coma (Rosanova *et al.*, 2012). TEPs in patients with unresponsive wakefulness syndrome/vegetative state were characterized by either a sleep-like slow wave response or no response (depending on patient and site of stimulation). Patients with brain injury offer a unique opportunity to record in the same patient EEG responses to TMS after stimulation of damaged/non-functioning cortical areas and healthy ones. If it is true that TEPs represent exclusively the responses of the cortical tissue to TMS, they will therefore be absent when dead cortical tissue is targeted and present otherwise, provided that the experimental procedures to reduce or abolish confounding factors such as auditory evoked potentials or muscle artifacts are implemented.

Methods

Patients

In the present study, three patients with severe brain injury were enrolled (Patient 1: male, 43 years old, anoxic etiology, 32 days post-injury; Patient 2: male, 19 years old, traumatic etiology, 172 days post-injury; Patient 3: 81 years old, ischemic stroke, 19 days post-injury). Repeated behavioral measurements of consciousness (four times a week, for one week, every other day) were obtained by trained and experienced neuropsychologists using the Coma Recovery Scale-Revised (CRS-R) (Giacino *et al.*, 2004; Schnakers *et al.*, 2008). The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liège and written informed consents were obtained by the patient's legal surrogates.

TMS targeting and stimulation parameters

All patients underwent one TMS/EEG session including six TMS/EEG measurements that differed for the site of stimulation. Cortical targets were identified on MRI scans acquired on a 3 T magnetic resonance scanner (Trio Tim, Siemens, Germany) using a T1-weighted MPRAGE sequence. The TMS stimulator consisted of a Focal Bipulse figure-of-eight coil (mean/outer winding diameter 50/70 mm, biphasic pulse shape, pulse length 280 ms, focal area of the stimulation 0.68 cm2) driven

by a Mobile Stimulator Unit (eXimia TMS Stimulator, Nexstim Ltd.). We controlled TMS parameters by means of a Navigated Brain Stimulation (NBS) system (Nexstim Ltd.) that employed a 3D infrared tracking position sensor unit to locate the relative positions of the coil and subject's head within the reference space of individual MRI scans. Navigated brain stimulation also calculated, online, the distribution and the intensity (expressed in V/m) of the intracranial electric field induced by TMS. The location of the maximum electric field induced by TMS on the cortical surface (hot spot) was always kept on the convexity of the targeted gyrus with the induced current perpendicular to its main axis. At least 300 trials were collected for each stimulation site. Stimulation was delivered with an interstimulus interval jittering randomly between 2000 and 2300 ms (0.4–0.5 Hz), at an intensity ranging of 140 V/m on the cortical surface; this intensity of stimulation is largely above the threshold (50 V/m) for an EEG response (Casali *et al.*, 2010, Komssi *et al.*, 2007, Rosanova *et al.*, 2009). The employment of the neuronavigation system allowed us to target precisely cortical sites within and outside lesions. In each patient, TMS was targeted bilaterally in both preserved and brain damaged regions encompassing frontal (superior frontal, precentral gyri), parietal (superior posterior parietal cortex) and occipital areas (superior occipital gyri).

EEG recordings

TMS/EEG measurements were performed using a TMS-compatible 60-channel amplifier (Nexstim Ltd). This device prevents amplifier saturation and reduces, or abolishes, the magnetic artifacts induced by the coil's discharge (Virtanen *et al.*, 1999). To further optimize TMS compatibility, the impedance at all electrodes was kept below 55kV. EEG signals were referenced to an additional electrode on the forehead, filtered (0.1–500 Hz) and sampled at 1450 Hz. Two extra sensors were used to record the electrooculogram. In the present study, most recordings were free from TMS-induced magnetic or electric artifacts and in all cases the EEG response was artifact-free starting from 10 ms after stimulation. Besides the magnetic artifact, other factors may confound the interpretation of TMS-evoked potentials, if not adequately controlled for. TMS may directly stimulate or activate trigeminal sensory afferents and head muscles evoking somatosensory potentials or muscle potentials, respectively. These artifacts were minimized by placing the coil on a scalp area as close as possible to the midline, far away from facial or temporal muscles and nerve endings. The 'click' associated with the coil's discharge that propagates through air and bone may also induce auditory evoked potentials artifacts. To overcome this issue, subjects wore earphones through which a noise masking, reproducing the time-varying frequency components of the TMS 'click', was played throughout each TMS/EEG session. Noise masking was also effective in preventing TMS from causing blinks or eye muscle reactions. Additionally, bone conduction of the TMS-associated 'click' was minimized by placing a thin foam layer between the coil and the EEG cap. As in previous studies, these procedures ensure genuine EEG responses to direct cortical stimulation with TMS (Ferrarelli *et al.*, 2010; Massimini *et al.*, 2005; Rosanova *et al.*, 2009; Rosanova *et al.*, 2012).

General experimental procedures

During each TMS/EEG session, patients were lying on their beds, awake and with their eyes open. If signs of drowsiness appeared, recordings were momentarily interrupted and subjects were stimulated using the CRS-R arousal facilitation protocols (Giacino et al., 2004). Throughout every recording session, the stability of stimulation coordinates was continuously monitored. If the virtual

aiming device was signaling a displacement >4 mm, the session was interrupted and the coil was repositioned. At the end of the experiment, the stimulation coordinates were recorded and the electrodes positions were digitized.

Data analysis and statistics

Data analysis was performed using Matlab R2006a (The MathWorks). First, TMS/EEG trials containing spontaneous blinks, eye movements or muscle artifacts were rejected using an automatic algorithm (Casali *et al.*, 2010). Then, EEG data were average referenced; down-sampled to half of the original sampling rate (725 Hz), band pass filtered (1–80 Hz) and baseline corrected over 300 ms prestimulus. Each TMS-evoked response was obtained by averaging 150–250 artifact-free trials.

To assess the threshold for significance at each EEG channel, a bootstrap method (Delorme and Makeig, 2004: Lv *et al.*, 2007: McCubbin *et al.*, 2008), which does not assume normal distribution of the observations, was applied. This method allowed to shuffle the time samples of prestimulus activity for each EEG channel (from -300 to -50 ms) at the single-trial level and to calculate 500 surrogated prestimulus time-series at each EEG channel. From each random realization, the maximum value across all latencies was selected to obtain the maximum distribution (control for type I error). Significance level was set at $P<0.01$.

PET measurements

In Patients 1 and 2, cerebral metabolic rates for glucose (CMRGlu) were measured by means of positron emission tomography (PET). Patients were monitored by two anesthesiologists throughout the procedure. Data were acquired after intravenous injection of 5–10mCi of [18 F]-fluorodeoxyglucose-PET (FDG-PET) on a Siemens CT scanner at the University Hospital of Liège, Belgium (Laureys *et al.*, 2000). Data were pre-processed and analyzed using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm) as described in previous studies (Bruno *et al.*, 2011; Laureys *et al.*, 1999).

Results and Discussion

TMS/EEG mappings were performed in three patients who have sustained severe brain injuries from different etiologies (anoxia, traumatic and ischemic lesions). According to the behavioral assessments, all three patients were diagnosed in an unresponsive wakefulness syndrome/vegetative state (The Multi-Society Task Force on PVS, 1994, Laureys *et al.*, 2010). They only showed reflexive behaviors and were unresponsive to environmental stimuli. By means of the neuronavigation system, we targeted TMS over cortical sites that were selected based on structural data (MRI scan) and functional data (PET scans).

Patient 1 suffered a prolonged cardio respiratory arrest (tens of minutes) that resulted in cerebral anoxia. Structural MRI scan using T1-weighted turbo spin-echo sequence clearly displays hyperintensities in deep structures such as lenticular nuclei, caudate nuclei, and left thalamus (Fig. 1, upper panel B), which are known to be markers of post-anoxic lesions (Ammermann *et al.*, 2007). PET scans (Fig. 1, middle and lower panel B) showed hypometabolic rates in large areas of the cerebral cortex and in both thalami, while metabolic rates were preserved in brainstem and cerebellum structures (as compared with healthy subjects). TEPs were recorded after stimulation of

six cortical sites (Fig. 1, panel A). Consistently with structural and functional data, TMS did not triggered any significant EEG response either under the coil or at distant sites since all stimulations were applied on brain damaged areas. These results clearly demonstrate that even in the presence of intact scalp and extrinsic eye muscle, it is possible to record TEPs that are clean from scalp muscle artifacts.

Patient 2 suffered from a head trauma during a boxing match. Structural MRI showed large post-contusion lesions with diffuse leucoencephalopathy confined to the left hemisphere. These lesions resulted in hypometabolic activity encompassing the left hemisphere (Fig. 1, upper panel D), while the right hemisphere was both structurally and functionally preserved (Fig. 1, right side of panel C and lower panel D). Consistent with these structural and functional data, TEPs were absent when three different cortical sites were stimulated on the left hemisphere (medial superior frontal, posterior parietal and superior occipital gyri) (Fig. 1, left side of panel C). On the contrary, TMS triggered significant sleep-like slow and simple EEG waves when the right hemisphere was stimulated at three preserved cortical sites (Fig. 1, right side of panel C). From the methodological standpoint, the case of Patient 2 is extremely informative as it offers a within-patient control for studying the neurobiological basis of EEG responses to TMS. Indeed, in the same patient, it was possible to record artifact-free TEPs both without and with significant EEG responses (from the injured hemisphere and from the unaffected hemisphere respectively) suggesting that the latter ones were purely reflecting the excitability of the cortical tissue under the TMS coil.

Patient 3 presented multiple strokes in both hemispheres that resulted in ischemic lesions. An acute lesion was confined to the right precentral gyrus and a large subacute lesion was observed in the left sylvian territory. By means of the neuronavigation system, we targeted two cortical sites over the right hemisphere: one over the injured cortical tissue and one over an unaffected region a few centimeters more medial than the injured one (Fig. 2, panel A). When TMS was applied over the lesion, the stimulation did not trigger any significant EEG response, whereas TMS evoked a significant, sleep-like EEG response when stimulating a healthy cortical site. Subsequently, we targeted four other cortical areas: one injured area and one healthy area of the left frontal lobe (Fig. 2, left side of panel B) and the right occipital lobe (Fig. 2, right side of panel B). Similarly to the TMS/EEG measurements performed over the right hemisphere, significant, sleep-like EEG responses to TMS were recorded only when the coil was targeted over an unaffected cortical area and absent otherwise.

Overall, our findings suggest that when confounding factors are appropriately controlled for and intact, functioning cortical areas are stimulated, TEPs purely reflect the response of the cortical tissue. Importantly, they also highlight that when one wants to measure cortical excitability and effective connectivity in brain-injured patients, a neuronavigation system must be employed in order to achieve an accurate targeting of the cortical areas.

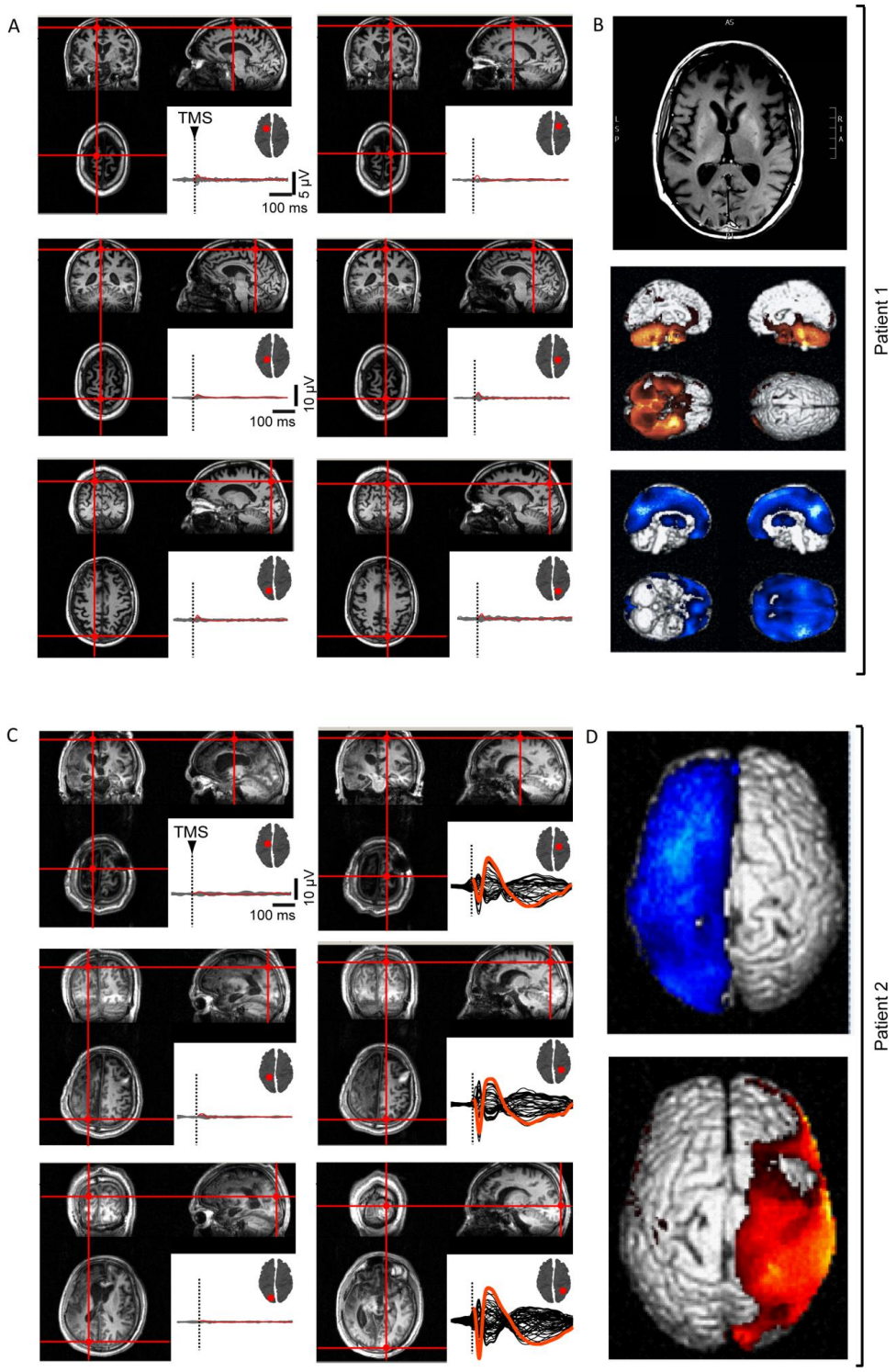


Figure 1: TEPs in cortical anoxia and brain trauma

Panel A shows structural MRIs (T1-weighted MPRAGE sequence) and cortical TMS targets (red crosshairs) as estimated by the NBS system in Patient 1 (anoxia). TEPs (butterfly plots of 60 EEG channels) recorded after the stimulation of six different cortical sites are shown for each site (left and right superior frontal gyri, left and right precentral gyri and left and right superior parietal gyri). Thin red traces indicate the EEG channel under the stimulator while gray traces indicate the other ones. No significant TEPs' components were detected (baseline bootstrap: $p<0.05$). Panel B shows a structural MRI scan (T1-weighted turbo spin-echo sequence) together with PET scans ([18 F]-fluorodeoxyglucose-PET) for Patient 1. Panel C shows

structural MRIs (T1-weighted MPRAGE sequence) and cortical TMS targets (red crosshairs) as estimated by the NBS system in Patient 2 (trauma) together with TEPs recorded after stimulation of six cortical areas. Significant TEPs components (black traces) are detected only when preserved areas are targeted and absent otherwise (gray traces). The channel under the coil is colored in red (thin trace=no response; thick trace=significant response).

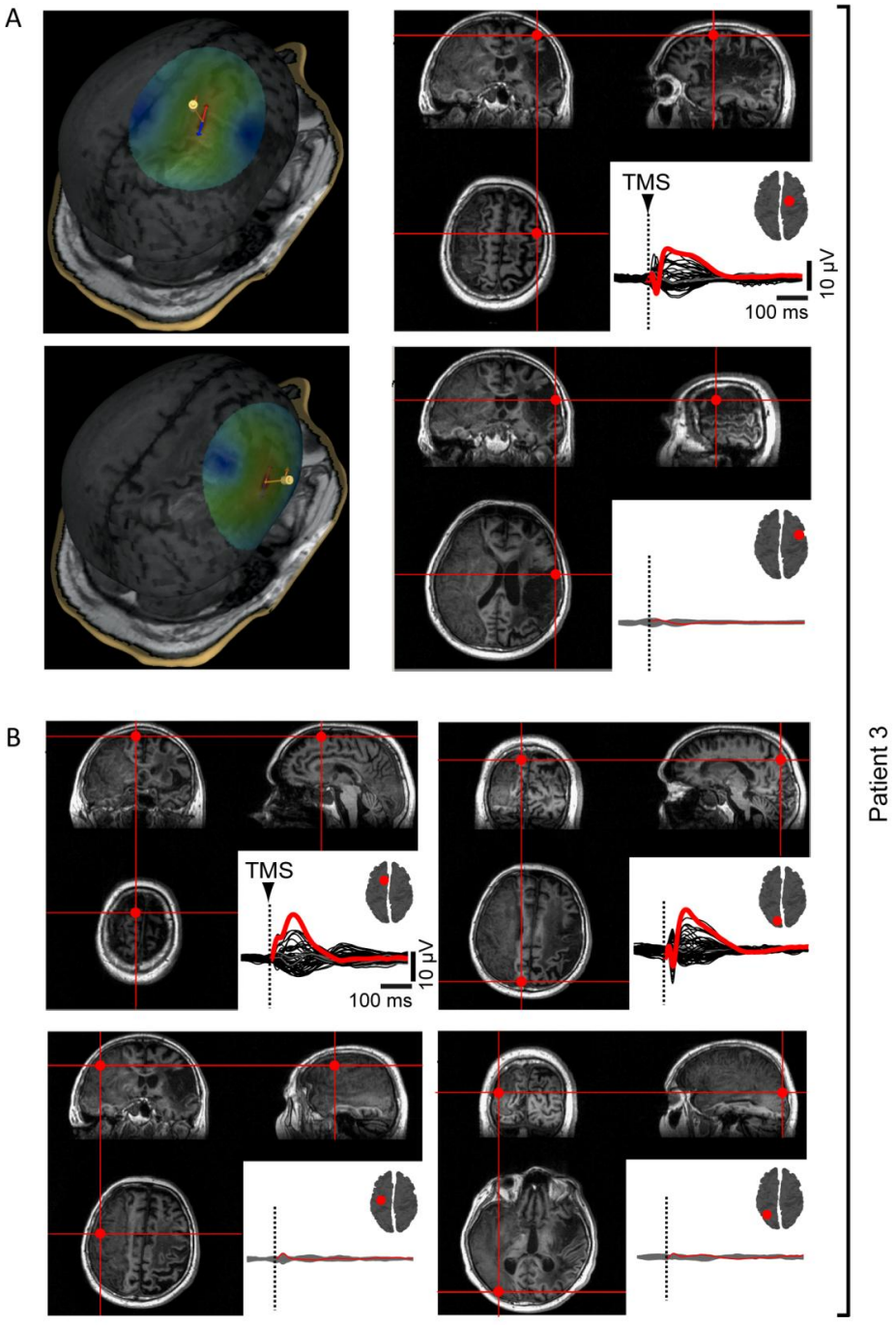


Figure 2: TEPs in cortical focal ischemia
Panel A shows two TMS cortical targets (one within and one outside a focal ischemic lesion in Patient 3) as displayed by the 3D neuronavigator software that was employed in the present study. The corresponding MRI scans and TEPs are also shown (black and thick traces for channels recording significant responses and thin gray and red traces for channels with no significant responses). Panel B shows further examples of targeting and TEPs within and outside ischemic cortical lesions.

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Burnout in healthcare workers managing chronic patients with disorders of consciousness

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Abstract:
Objectives. The aim of this study was to assess the presence of burnout among professional caregivers managing patients with severe brain injury recovering from coma and working in neuro-rehabilitation centres or nursing homes.
Methods. The Maslach Burnout Inventory was sent to 40 centres involved in the Belgian federal network for the care of vegetative and minimally conscious patients. The following demographic data were also collected: age, gender, profession, expertise in the field, amount of time spent with patients and working place.
Results. Out of 1068 questionnaires sent, 568 were collected (53% response rate). Forty-five were excluded due to missing data. From the 523 healthcare workers, 18% (n=93) presented a burnout, 33% (n=171) showed emotional exhaustion and 36% (n=186) had a depersonalization. Profession (i.e. nurse/nursing assistants), working place (i.e. nursing home) and the amount of time spent with patients were associated with burnout. The logistic regression showed that profession was nevertheless the strongest variable linked to burnout.
Conclusions: According to our study, a significant percentage of professional caregivers, and particularly nurses, taking care of vegetative and minimally conscious patients presented burnout. Prevention of burnout symptoms among caregivers is crucial and is expected to promote more efficient medical care of these challenging patients.

Keywords: emotional exhaustion, depersonalization, vegetative state, minimally conscious state.

Introduction

Working with patients in a chronic vegetative or minimally conscious state is a real clinical challenge. Vegetative state, newly called 'unresponsive wakefulness syndrome', is characterized by the presence of arousal in absence of awareness showing only reflexive motor responses [1, 2] whereas the minimally conscious state has been defined by the presence of inconsistent but reproducible goal-directed behaviours [3]. Some of these patients remain for many years in those states without being able to communicate with the outside world. Hence, their medical management might have a significant psychological impact on healthcare teams. Indeed, the importance of motor (e.g. paralysis and severe spasticity), physiological (e.g. tracheotomy and gastrostomy) and cognitive (e.g. memory disorders, aphasia or lack of adequate communication) deficits involves intensive management. In light of patients' full dependence on the medical team for all daily activities, the practical and emotional challenges caregivers are faced with are evident. The emotional aspect is of particular importance when one considers the low chances of recovery in this patient's population, the risks of life-threatening medical complications, the possible premature death of patients and potential conflicts with families. All these components can contribute to serious psychological distress and more particularly to burnout [4].

Burnout syndrome can be defined by physical and psychological emotional exhaustion, depersonalization and a low sense of personal accomplishment [4]. This syndrome occurs in response to both physical and psychological stress encountered in the workplace and is relatively common in professionals taking care of patients with critical illness, particularly in medical areas such as psychiatry, geriatric, oncology, emergency, surgery and intensive care units [5-9]. Burnout may decrease quality of life of healthcare professionals, generating symptoms such as anxiety, irritability, mood swings, insomnia or sense of failure. It has also been associated with substance abuse, early retirement, physical illness, absenteeism, depression and even death [10-12]. Caregivers work in emotionally charged situations that may lead to conflicts with patients, their families and other members of the medical staff [13]. All those factors result in decreased quality of care and patients' safety [14, 15].
Some studies suggest that stress observed in nursing staff working in rehabilitation services may be related to the diagnosis of the patients and the severity of the lesions [16, 17]. Another study including 16 caregivers working with vegetative state patients showed that the level of anxiety and depression was correlated with unsatisfactory relationship with family and possible death of the patients [18]. However, specifically the presence of burnout among medical teams managing vegetative and minimally conscious patients has never been investigated. Therefore, we decide to assess the burnout in healthcare workers managing severely brain-damaged patients with impaired consciousness.

Methods

Forty institutions (neurorehabilitation centres and nursing homes) involved in the Belgian federal project on the management of patients with impaired consciousness were contacted in order to obtain their consent to participate in the study. Following agreement, the Maslach Burnout Inventory (MBI; French or Dutch version) [4], a standardized questionnaire

assessing burnout syndrome, was sent by regular mail together with a form explaining the aim of the study. Participants were asked to fill the questionnaire only whether they wanted to participate to the study. The questionnaire was anonymously completed and was returned by the referent of each institution. This procedure was approved by the ethics committee of the Faculty of Medicine, University of Liège in Belgium.

The MBI questionnaire, which has become the 'almost universally accepted gold standard to assess burnout' [19] due to its high reliability and validity [4, 20], consists of 22 personal statements in which participant has to estimate the frequency at the professional level on a seven-point Likert scale, ranging from never experiencing those feelings (0 points) to having those feelings every day (7 points). The total score varies from 0 to 132. The questionnaire measures three components of burnout: emotional exhaustion, depersonalization and personal accomplishment. The emotional exhaustion subscale contains nine items such as 'I feel emotionally drained by my work' with a score varying from 0 to 54. The depersonalization subscale includes five items such as 'I do not really care what happens to my patients' with a score from 0 to 30. The personal accomplishment subscale is composed of eight items such as 'I have accomplished many worthwhile things in this job' with a score ranging from 0 to 48. Each of the three components was divided into low, moderate and high level according to the recommendation of the authors of the MBI. High mean scores on emotional exhaustion and depersonalization scales and low mean scores on personal accomplishment are suggestive of burnout [21]. Because personal achievement does not always correlate negatively with the first two subscales, it was removed specifically from the determination of level of burnout. Burnout was here considered moderate if the participant had a score >26 at the emotional exhaustion scale or a score >9 at the depersonalization scale, and a high burnout was considered if the participant had both a score >26 at the emotional exhaustion scale and a score >9 at the depersonalization scale [4, 5, 12].

The following demographics data were also collected: age, gender, profession (i.e. physician, nurse, nursing assistant, physio/speech/occupational therapist or psychologist/social worker), expertise in the care of patients with disorders of consciousness (i.e. <4 years, between 4 and 9 or >9 years), amount of time spent with these patients (i.e. hours per week) and working place (i.e. neurorehabilitation centre or nursing home).

Statistical analyses were performed using STATA software (Stata Statistical Software; Release 11. College Station, TX: StataCorp LP 2009). A series of Chi-square tests were conducted to determine if the proportion of participants was higher depending on the presence or absence of burnout for the following variables: gender, profession, expertise and working place (table 1). Kruskal-Wallis tests were also performed to determine if the age of the caregiver and the time spent with patients were different depending on the presence or absence of burnout. Same analysis using Chi-square and Kruskal-Wallis tests were replicated for the three sub-components of burnout (i.e. emotional exhaustion, depersonalization and personal accomplishment) (table 1). Finally, a multivariate analysis with a logistic regression (stepwise backward selection) was performed to highlight the variables associated with burnout. Results were considered significant at $p<0.05$.

Results

All centres included in the federal project participated in the study. From the 1068 sent questionnaires, 568 were collected (53% response rate). Forty-five questionnaires were removed from the analysis due to too many missing responses or unclear answers. 523 questionnaires were therefore included in the analysis. The average age of participants was 37 SD 10 years (449 women) and the average time spent with severely brain-damaged patients was 19 SD 14 hours per week. Table 1 shows the percentage of participants for the working place, the profession and the expertise.

Variables	Sub-category	Participants
Working place	neurorehabilitation centre	44%
	nursing home	56%
Profession	physician	5%
	nurse	47%
	nursing assistant	21%
	physiotherapist	11%
	speech therapist	2%
	occupational therapist	8%
	psychologist	3%
	social worker	3%
Expertise	<4 years	44%
	between 4 and 9 years	40%
	>9 years	16%

Table 1 – Participants' demographics (n=523) according to working place, profession and expertise.

According to the MBI questionnaire, 93 participants presented a burnout (18%). A moderate burnout was observed in 76 responders (15%) and 17 caregivers (3%) showed a severe burnout (figure 1). Moderate to high emotional exhaustion was present in 171 participants (33%) and moderate to high depersonalization in 186 responders (36%). Personal accomplishment was considered low in 15 participants (3%) (table 2). Among the burnout responders, 63 out of 93 (68%) presented a high emotional exhaustion, 47 (50%) had a high depersonalization and 10 (11%) showed a low personal accomplishment.

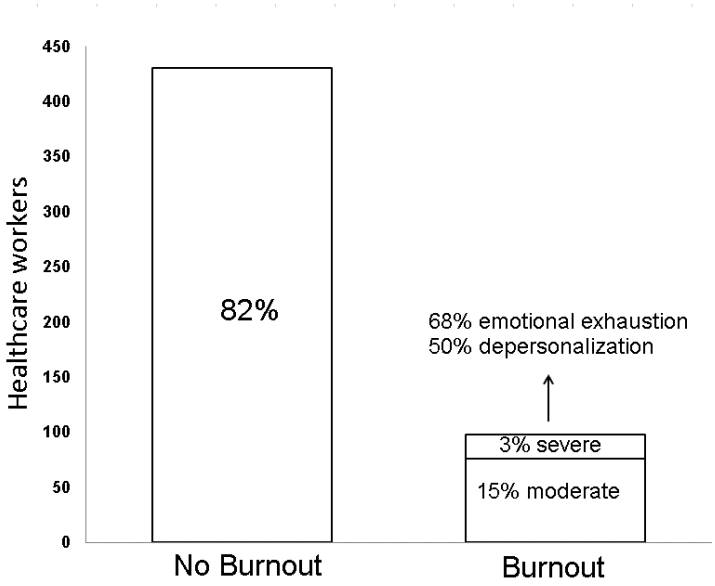


Figure. 1 – Percentage of burnout among the 523 questionnaires included in our analyses

	Low	Moderate	High
Burnout	82%	15%	3%
Emotional exhaustion	67%	21%	12%
Depersonalization	64%	27%	9%
Accomplishment	3%	12%	85%

Table 2 – Percentage of burnout and its three subcomponents among all participants

Globally, a difference between proportions of participants with and without burnout was found for the profession (table 3). Burnout was higher among nurses (24%) and nursing assistants (23%) than other occupations (8.5%). The time spent with patients was also a factor of burnout with burnout participants spending more time with patients (23h±14h) than participants who did not present the syndrome (18h±14h). Finally, a difference was also observed for the working place with more burnout in nursing homes (23%) than in rehabilitation centres (14%). No significant result was obtained for the age, gender and expertise (table 4).

For the emotional exhaustion subcomponent, only a difference for the profession was observed with nurses and nursing assistants presenting more exhaustion than other jobs. No significant result was obtained for the other variables (i.e. working place, age, gender, expertise and time) (table 4).

For the depersonalization subcomponent, no difference between proportions for the profession was obtained. However, the proportion of participants with high depersonalization was greater among nurses and nursing assistants (12%) as compared to other professions (4%). A difference according to the time was also measured with a greater number of hours spent with patients for participants with high depersonalization (27h±13h) than for participants with a low (18h±14h) to moderate (19h±13h) depersonalization. No significant result was obtained for the working place, age, gender and expertise (table 4).

For the personal accomplishment subcomponent, no difference was obtained for the profession. The proportion of responders with a low achievement seemed nevertheless greater among nurses and nursing assistants (3%) than for other professions (0.2%). A difference in the age was also found with a lower age for participants with higher personal accomplishment (37±10) than for participants with a low to moderate personal accomplishment (40±9). A difference was also obtained depending on the time spent with patients, the number of hours being less important for participants with a high personal accomplishment (18h±13h) than for participants with a low (36h±7h) or moderate (22h±15h) personal accomplishment. No result was found for the working place, gender and expertise. Table 4 shows the chi-square values and p-values for the burnout and its three subcomponents (emotional exhaustion, depersonalization and personal accomplishment).

Finally, logistic regression showed that the profession was the most associated variable with the burnout (more exactly nurses and nursing assistants) ($z=2.63$; $p=.009$).

Profession	Burnout
Physician	8%
Nurse	24%
Nursing assistant	23%
Physio-/speech-/ergo-therapist	8%
Psychologist/social worker	10%

Table 3 – Healthcare workers presenting a burnout (count and percentage)

	Burnout		Emotional exhaustion		Depersonalization		Personal accomplishment	
	Chi2	P-value	Chi2	P-value	Chi2	P-value	Chi2	P-value
Working place	6.6	0.01*	4.3	0.11	1.16	0.56	3.8	0.15
Profession	20.1	<.0001*	20.5	<0.009*	11.9	0.15	12	0.15
nurse/nursing assistant	19.9	<.0001*	18.3	<0.0001*	8.8	0.012*	8.61	0.014*
Time	5.7	<.02*	0.29	0.86	10.8	0.005*	11.82	0.003*
Age	0.5	0.48	0.28	0.87	4.89	0.09	6.22	0.04*
Gender	0.94	0.33	0.53	0.77	3.64	0.16	4.6	0.1
Expertise	0.04	0.98	7.12	0.13	3.9	0.4	4.8	0.31

Table 4 – Chi-square statistics and p-values for the burnout and its three subcomponents as regards the working place, profession, age, gender and expertise

Discussion

The aim of this study was to evaluate the prevalence of burnout among healthcare workers taking care of patients with severe disorders of consciousness. Our results showed moderate to high burnout in 18% of the participants (defined by a severe emotional exhaustion and/or a severe depersonalization) suggesting that almost one out of 5 members of the medical team could potentially suffer from this condition. This is particularly preoccupying as burnout leads to high rates of absenteeism, lower productivity and represents a significant cost in terms of healthcare [22]. Previous studies using the MBI reported widely varying burnout rates among medical and paramedical team, ranging from 15 to 82% [10, 14, 23-26]. For instance, in several studies, prevalence for burnout in anesthesia and critical care medicine was present in about 30% of nurses and approximately 40-50% among physicians [27, 28]. This discrepancy can be explained by the important methodological heterogeneity existing across studies (i.e. recruitment, population, used scale, cut-off score, burnout definition, etc.) [10, 23, 24]. Similar results have been reported in oncology wards [29] where the level of environmental stress is important, as it can be the case when dealing with non communicating severely brain-damaged patients.

On the other hand, one third of healthcare workers (33%) showed moderate to severe emotional exhaustion. This component has been previously related to workload [30] and qualitative job demands in combination with low job resources (e.g. autonomy, social support, supervision relationship and performance feedback) [31]. Moreover, in our study, one third (36%) of the responders also presented moderate to severe depersonalization. These last two results are in line with previous medical studies. Indeed, prevalence of emotional exhaustion and depersonalization among cancer care provider studies seems to be around

36% and 34% respectively [29]. Among medical residents, emotional exhaustion has been shown to be around 41 to 50% and depersonalization around 34 to 70% [23]. Another study including nurses from different specialties reported 23% of emotional exhaustion and 5% of depersonalization [5]. Finally, 3% of our sample presented a low personal accomplishment, with nevertheless an increase to 11% when assessing burnout participants only.

According to our analyses, the variable profession was the most associated with burnout. Nurses and nursing assistants were more likely to present a burnout (respectively, 24 and 23%) than physicians, speech/occupational or physio-therapists, psychologists or social workers (8 to 10%). Consistently, the proportion of emotional exhaustion, depersonalization and low personal accomplishment was also greater for those professions in the univariate analysis. Given the nature (e.g. tasks, proximity and time spent with patients) and emotional demands, the nursing team is most likely to develop burnout [5]. The syndrome may be subsequent to a deterioration of relations with the medical team or difficult relationship between nurses and patients or patients' family. Several studies have also shown that, despite a very positive image of the profession, the majority of nurses in Belgium reported an insufficient teamwork, organizational support and social recognition [32]. Moreover, an international study showed that higher levels of burnout among nurses were associated with lower ratings of quality of care [33].

Burnout also seemed higher according to the time spent with non communicating patients. Indeed, the more important the time spent with patients, the greater is the number of healthcare workers with a burnout, as previously observed [28]. Moreover, the number of hours worked in a stressful environment may participate in burnout [6]. The proportion of participants with burnout was also more important according to the place of hospitalization and, more particularly, in nursing homes. This result could be explained both by the type of population and by the initial training of the medical staff practicing in nursing home. Indeed, healthcare workers must deal with chronic patients often young who are no longer evolving and whose prognosis is often limited. Because these patients remain in these institutions for a long time, the hope of recovery fades as time goes by and grief may be experienced by caregivers. Additionally, the healthcare team mainly takes care of elderly patients and may feel helpless when faced with management of severely brain-damaged patients who need specific care they may not be familiar with. Inadequate preparation [34] and exposure to death [30] can therefore lead to burnout. It is nevertheless difficult to disentangle if burnout is the consequence of working with severe brain injured patients or more generally the results of working with elderly patients. Further studies should be investigated to answer this question. Meanwhile, recent studies have shown the importance of developing skills in geriatric units in order to prevent emotional exhaustion [7, 35]. Finally, the number of participants with low personal accomplishment was higher in terms of age, younger caregivers having a higher personal accomplishment than older ones. Some studies have highlighted age as a predictive factor of burnout [36] but the relationship between age and burnout is still not clear [37], suggesting that more research is warranted.

Our study is the first to investigate burnout in caregivers of severely brain-injured patients with disorders of consciousness. Considering the average response rate (53%), we should however be cautious with the generalization of the findings. One could argue that the percentage of responders among the different professions managing patients recovering from coma was not homogeneous (i.e. more nurses filled in the questionnaires compared to other occupations) which could amplify and/or minimize the effect of burnout within a profession. Nevertheless, our statistical analysis took into account this parameter. Besides, our sample is representative of the composition of a typical medical team as the number of nurses/nursing assistants is usually higher than other professions (such as physicians, speech/occupational or physio-therapists, psychologists or social workers). One could also argue that this study took place in Belgium and could therefore lead to bias based on organizational and governmental issues. Comparison between studies performed in various countries is complicated as findings may differ as a result of differences in cultural, educational and organizational backgrounds [23]. We nevertheless need further investigation to confirm our results and to generalize them across countries and professions.

In conclusion, about one out of five caregivers in this study suffered from burnout. Burnout affects caregivers' wellbeing and therefore the quality of care that may be provided to the patients. Treatment and prevention of burnout are needed to increase the medical staff's quality of life and productivity. There are nowadays no preventive or therapeutic measures which could meet the scientific requirements for guidelines [27]. However, several studies highlighted the importance of an effective adjustment (i.e. relaxation, cognitive strategies, communication skills, problem solving and capacity building of adjustment to stressful situations), a sufficient social support and an appropriate organizational structure to maintain professional satisfaction and good quality of care [38, 39]. For example, regular team meetings and supervision sessions may improve the social climate in hospitals and enhance communication [40]. Detecting signs of chronic stress disorder such as work overload and value conflict should be considered as a priority to prevent burnout among medical and paramedical team working with disorders of consciousness.

Acknowledgement

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Needs in relatives of patients with disorders of consciousness

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ABSTRACT

Objective. To evaluate the need for medical information, involvement in care as well as emotional, social, instrumental and professional supports in relatives of vegetative (VS) and minimally conscious (MCS) patients. **Methods**. The Family Needs Questionnaire was sent to the next of kin of patients being at home or hospitalized in forty Belgian institutions (i.e., neuro-rehabilitation centers and nursing homes). **Results**. We collected 89 questionnaires. Participants reported to be largely unsatisfied for the following domains: emotional (88%) and social support (77%) as well as medical information (71%). Among the participants, 82% presented depressive thoughts, 73% reported the presence of anxiety, and 19% were considering end-of-life decision for their relative. Moreover, participants who expressed considering end-of-life decision were significantly less satisfied with their emotional needs. **Conclusion**. For relatives of VS and MCS patients, receiving complete, clear and simple medical information as well as adequate social and emotional support were considered to be fundamental but those needs were often unmet. Insufficient consideration of these needs may lead to psychological distress and may favor irreversible choices, such as end-of-life decisions. **Keywords**. brain injury, family needs, relatives, next of kin, vegetative state, minimally conscious state.

INTRODUCTION

Thanks to progress in intensive care, an increasing number of severely brain-injured patients is currently surviving their injuries but may remain in coma. The majority of these patients recovers from coma, evolving towards a vegetative state (1) (i.e., arousal without signs of awareness; also called the "unresponsive wakefulness syndrome") (2) before recovering partial (i.e., minimally conscious state; i.e., presence of inconsistent but reproducible goal-directed behaviours) or complete consciousness (3). Some patients can also remain in a vegetative state or in a minimally conscious state for years. The proportion of chronic patients recovering from coma is estimated to 46 per million in the United States, 36 per million in Belgium and 14 per million in Great Britain (4-5). Although there is an increasing interest in the study of patients with disorders of consciousness in the last years (6) with clinical, ethical, legal and scientific implications (7), little attention has been paid on the relatives of post-coma non-communicating survivors. The relatives of these patients have to face a particularly difficult situation. They may experience a broad variety of emotions ranging from shock to depression, through guilt, denial, anxiety and hostility directed to the medical staff (8). Beside the emotional aspects, they need to comprehend various medical information, manage the cost of medical care and, sometimes, consider end-of-life options (9). Assessing and meeting the needs of severely brain-injured patients' relatives is crucial for them to enhance their ability to cope with the high level of stress generated by the situation they live and eventually improve their quality of life. Only one study aimed at investigating vegetative or minimally conscious patients' relatives needs. In that study, the authors showed a significant level of anxiety and depression in the relatives of patients diagnosed as being in a persistent vegetative state (10); it was however limited to assess emotional aspects only. The objective of the present study was to evaluate various needs (such as the need for medical information, for emotional, social, instrumental and professional support as well as for the involvement in care) in relatives of patients recovering from coma and hospitalized in neuro-rehabilitation centers, nursing homes or staying at home.

METHODS

Experimental procedure. The next of kin of patients were contacted for participation to the study. Patients were at home or hospitalized in one of the neuro-rehabilitation centers (n=21) and nursing homes (n=19) involved in the Belgian federal network for the care of vegetative and minimally conscious patients (5). The "Family Needs Questionnaire" (FNQ) (12) was sent by regular mail to each participant, accompanied by a form explaining the aim of the study. Participants were explicitly asked to fill the questionnaire only whether they wanted to participate to the study. The questionnaire was anonymously completed at the institution and was returned by the referent of each institution; when sent at relatives' homes, it was returned by the relative him/herself. The FNQ is a standardized and validated questionnaire allowing the assessment of needs of the relatives of patients suffering an acquired brain lesions (12, 26-27). It evaluates needs for medical information, emotional, social, instrumental and professional support as well as involvement in care. The questionnaire consists of 37

statements expressing the needs under investigation here (e.g., "I need to have explanation from professionals given in terms I can understand"). The participants were also asked to estimate the importance of each need on a scale ranging from 1 (not important) to 4 (very important) and to mention whether the specific need was completely (Y), partly (P) or not (N) satisfied. Additionally to the questionnaire, demographic information was collected, such as the patient's age and level of consciousness (i.e., vegetative state, minimally conscious state or emergence from minimally conscious state), the setting (i.e., neuro-rehabilitation center, nursing home or home), the time elapsed since injury as well as the next of kin's age and gender and his/her relationship to the patient (i.e., husband/wife, father/mother, brother/sister, son/daughter or friend). The next of kin also had to rate the presence of anxiety (i.e., absence or presence), depressive thoughts (i.e., absence or presence) and whether they were considering end-of-life decision for their relative (i.e., yes or no). The study was approved by the Ethical committee of the Faculty of medicine of the University of Liège.

Statistical analyses. Participants' responses were pooled in two dichotomous variables, one based on the importance of each need (important/very important versus slightly/not important) and the other based on satisfaction of each need (satisfied versus partially/not satisfied). Questions were also pooled according to the need to which these were related to (12**).** We used the median of the responses for each pool of questions (i.e., each need) in order to report the proportions within each dichotomous variable (i.e., satisfaction and importance). We performed binomial tests in order to detect differences in proportions. We used the sum of these responses to perform further analyses (12**)**. Kruskal-Wallis tests were applied to detect differences in the level of importance (important vs. not important) and in the level of satisfaction (satisfied vs. not satisfied) attributed to each need as a function of the patient's level of consciousness, the next of kin's gender and his/her relationship with the patient, the setting, the presence of anxiety, depressive thoughts and end-of-life decision. Spearman's rank order correlations were computed to assess the relationship between the level of importance and the level of satisfaction attributed to each need and the patient's age, the time elapsed since the brain lesion and the next of kin's age. We also performed Chi-square analyses in order to test the difference in the proportion of participants reporting anxiety, depressive thoughts and end-of-life decision as a function of the patient's level of consciousness, the next of kin's gender and his/her relationship with the patient, and the setting. Finally, we used Kruskal-Wallis tests to detect differences in the patient's age, the time elapsed since the brain lesion and the next of kin's age as a function of the presence/absence of anxiety, depressive thoughts and end-of-life decision. We only reported significant results (i.e., $p<.05$, corrected with Bonferroni test).

RESULTS

Out of the 193 questionnaires sent out, 89 valid questionnaires were returned. The next of kin's age was 51±13 years (56 women). The relationship with the patient was more frequently father/mother (44%) and less frequently husband/wife (29%), son/daughter (15%), brother/sister (11%) or friend (1%). The patients were on average 45±16 years old, presented

a disorder of consciousness between one month to 28 years and were hospitalized in a neuro-rehabilitation center (34%), in a nursing home (51%), or were staying at home (15%). Patients were considered as being in a vegetative state (24%), in a minimally conscious state (56%) or as emerging from the minimally conscious state (20%). The needs rated the most frequently as being important to very important were the need for medical information (99%), the need for involvement in care (90%) as well as the need for social (89%) and emotional (76%) support as opposed to the needs for instrumental (25%) or professional (13%) support (Figure 1). We observed a negative correlation between the level of importance attributed to the need of medical information and the patient's age (r=-.30; p=.01). The level of importance attributed to this need also differed according to the relative's gender (H=5.8; p=.01), women rating medical information as more important than men. The needs with a significantly higher percentage of dissatisfaction were the need for medical information (71%), the need for social support (77%) and the need for emotional support (88%) as opposed to the needs for involvement in care (55%) (Figure 1). A negative correlation was obtained between the level of satisfaction for emotional support and the next of kin's age (r=-.44; p=.01), older participants rating emotional support as being less satisfied than younger ones. Additionally, we found a positive correlation between the level of satisfaction for both emotional and social support (r=.75; p<.001). With respect to psychological distress, 73% of respondents reported the presence of anxiety, 82% reported depressive thoughts and 19% were considering end-of-life decision for their relative. Interestingly, we observed that dissatisfaction with emotional support had a tendency to be higher when the next of kin was considering end-of-life decision (H=3.87; p<.05) (Figure 2). Beside, Chi-square analyses revealed that considering end-of-life decision was different according to patient's consciousness level (X=14.1; p=.001) and the setting (X=11.87; p=.001). This was particularly frequent when the relative was in a vegetative state (62%) and hospitalized in a nursing home (88%) (Figure 2).

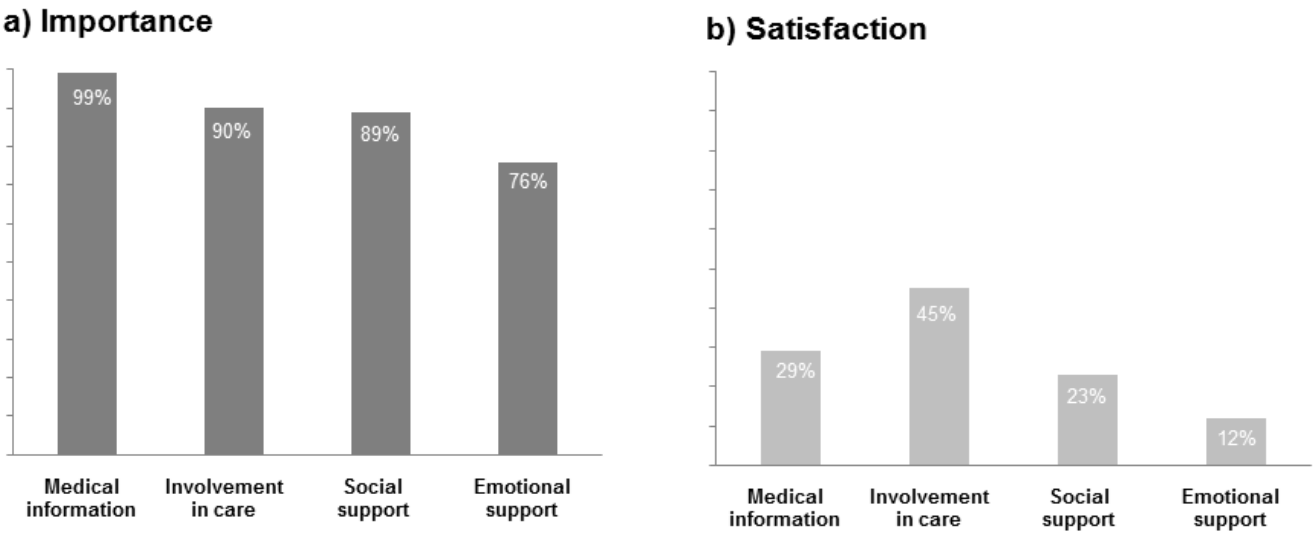


Figure 1. Percentage of participants considering the need for medical information, involvement in care as well as social and emotional support as (a) important to very important and as as (b) satisfied.

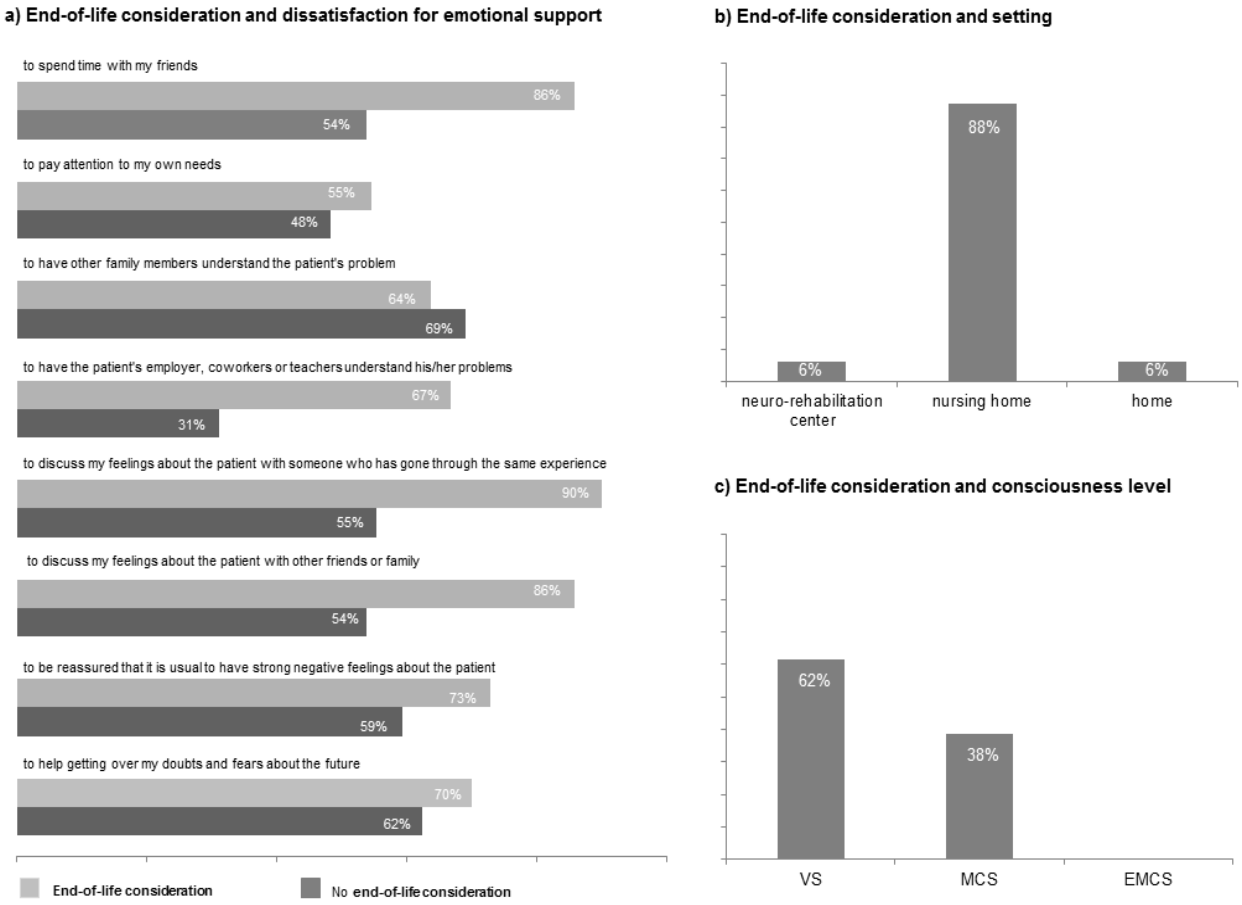


Figure 2. Percentage of participants considering end-of-life for their relative according to (a) the dissatisfaction of the need for emotional support (for each FNQ statement related to this need), (b) the setting and (c) the relative's consciousness level (vegetative state – VS, minimally conscious state – MCS, emergence from MCS – EMCS).

DISCUSSION

The objective of this study was to assess the needs of severely brain-injured patients' relatives. Our results showed that the need for medical information as well as for social and emotional support were considered as important to very important while being at the same time unmet to a high degree.

The need for medical information was considered to be the most important need (99%). The importance of this need however differed according to the patient's age and the next of kin's gender. First, the need for medical information appeared to be more important for relatives of young patients. As previous studies have associated increasing age with poorer outcome in patients with brain injury (11, 1), relatives of young patients probably have stronger expectations as regards the patient's recovery and a stronger will to follow his/her medical status more closely. Second, this need appeared to be more important for women, suggesting

that they need, more than men, to be informed on treatment and physical/cognitive progresses as well as to be reassured that the best medical care is provided (12). The need for medical information was nevertheless unsatisfied in 71% of the participants. This need has previously been reported to be one of the most central needs of brain-injured patients' relatives (13-15). This is an important finding since providing clear and accurate information may significantly reduce stress and increase coping abilities (15). Poor medical information or poor adjustment to medical information may potentially lead to hostility and complaints towards the medical staff that, in turn, can contribute to burnout (8, 16). On the other hand, the most unsatisfied need was the need for emotional support (88%), particularly for the older next of kin. We found a high rate of participants presenting anxiety (73%) and depressive thoughts (82%) which is linked to what has been observed in previous studies (10, 13, 17-20). This emotional need was also linked to the satisfaction of the need for social support suggesting that avoiding poor social adjustment (18, 19) and social isolation (10) could participate to a higher satisfaction at an emotional level. Satisfaction for the emotional support seems an important factor which could influence discussions on treatment limitation options in these patients. Indeed, we here showed that participants considering end-of-life decision (19%) tend to present higher dissatisfaction for the need of emotional support. Hence, accurate detection and resolution of these issues is fundamental in order to alleviate suffering and avoid inadequate medical decision. The frequency of end-of-life preferences making was higher when the patient was considered as being in a vegetative state (61%). This is in line with what we previously showed in a European survey among healthcare workers (n=2475) (21). Indeed, treatment withdrawal (i.e., artificial nutrition and hydration) was considered more frequently in case of vegetative patients (66%) than in case of minimally conscious patients (28%). However, in our study, only 19% of the participants would consider end-of-life decision for their relative. This illustrates the difference of opinions between clinicians and families. It stresses the importance for clinicians to explain clearly to the family the patient’s medical status for giving them the opportunity to take adequate decisions but also to avoid anticipating family’s decisions as these may be different from what professionals would imagine.

The frequency of end-of-life decision making was also higher when the patient was in a nursing home. This may be related to the fact that patients in nursing homes, as compared to patients in a rehabilitation center, are mainly chronic patients who usually show few signs of improvement. Additionally, these nursing homes are often primarily designed for disabled elderly people and hence the type of care that is provided may not correspond to the relatives' expectations (22).

In conclusion, providing complete, clear and simple medical information as well as sufficient emotional and social support is essential for the relatives of patients with disorders of consciousness. According to our results, all these needs are mostly unmet. In parallel to the high percentage of anxiety and depressive thoughts we have found, the least satisfied need was the emotional support. Low satisfaction of this need was related to considerations of end-of-life decisions. The assessment and satisfaction of this need are therefore crucial. The development of interventions, such as individual psychotherapy (where the relatives can freely express their feelings), group therapy (where the relatives can meet and share their

experiences with each other's) or formal information sessions (where the relatives can better comprehend the situation they are facing) has been shown to be particularly helpful for traumatic patients' relatives as these may increase coping abilities, reduce stress, and hence improve their quality of life (23, 24). The utility of these interventions would nevertheless have to be tested and validated in relatives of patients with disorders of consciousness. Note that our results could have been influenced by a selection bias as only 89 out of 193 questionnaires were returned (46%) but also, as shown previously, by cultural (21) and personal opinion (25). In the future, international multi-centric studies would hence be needed in order to better define the daily life needs, challenges and effective interventions for families of patients with disorders of consciousness.

CONFLICT OF INTERESTS

The authors do not have any conflict of interests or financial disclosures to declare.

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Chapter 2
Disorders of Consciousness: Coma, Vegetative and Minimally Conscious States

Olivia Gosseries, Audrey Vanhaudenhuyse, Marie-Aurélie Bruno, Athena Demertzi, Caroline Schnakers, Mélanie M. Boly, Audrey Maudoux, Gustave Moonen, and Steven Laureys

Abstract Consciousness can be defined by two components: arousal and awareness. Disorders of consciousness (DOC) are characterized by a disrupted relationship between these two components. Coma is described by the absence of arousal and, hence, of awareness whereas the vegetative state is defined by recovery of arousal in the absence of any sign of awareness. In the minimally conscious state, patients show preserved arousal level and exhibit discernible but fluctuating signs of awareness. The study of DOC offers unique insights to the neural correlates of consciousness. We here review the challenges posed by the clinical examination of DOC patients and discuss the contribution of functional neuroimaging and electrophysiological techniques to the bedside assessment of consciousness. These studies raise important issues not only from a clinical and ethical perspective (i.e. diagnosis, prognosis and management of DOC patients) but also from a neuroscientific standpoint, as they enrich our current understanding of the emergence and function of the conscious mind.

Keywords Brain injury • Coma • Consciousness • Electrophysiology • Functional neuroimaging • Locked-in syndrome • Minimally conscious state • Prognosis • Treatment • Vegetative state

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2.1 Introduction

In recent years, resuscitation techniques have led to a considerable increase in the number of patients who survive severe brain injuries. Some patients recover in the first days after the accident while others die quickly. Others, however, recover more slowly through different stages before fully or partially recovering consciousness. Patients in altered states of consciousness present major challenges concerning the diagnosis, prognosis and daily care. Indeed, detecting signs of consciousness is not always easy and, in some cases, they may remain unnoticed. Some of these signs are of prognostic importance. Prognosis, in turn, may influence therapeutic choices. The interdependency of these factors cannot be ignored: the announcement of a favorable outcome may imply the commitment of the medical team, while a bad prognosis may jeopardize the patient's potential recovery. End-of-life decisions, aggressive therapy with analgesic drugs and discussion about options of euthanasia often arise and, in many cases, lead to difficult debates among the medical staff, and sometimes more widely through the media and society.

2.1.1 Two Components of Consciousness

Clinically defined, consciousness encompasses two main components: arousal and awareness (Zeman 2001). At the bedside, arousal (also called vigilance or alertness) is observed by looking at the presence of eye opening. At a neuroanatomical level, the level of arousal (and in particular of sleep-wake cycles) is mainly supported by the brainstem (which is the region between the brain and the spinal cord), and the thalami (which are the nuclei in the center of the brain) (Schiff 2008; Lin 2000).

Awareness, the second component of consciousness, refers to conscious perception which includes cognition, experiences from the past and the present, and intentions. At a clinical level, awareness is mostly inferred by command following (e.g. "squeeze my hand", "close your eyes"). At a neuroanatomical level, awareness is underpinned by the cerebral cortex, which is a thin mantle of gray matter covering the surface of each cerebral hemisphere, and mainly through a wide frontoparietal network (see Sect. 3.2.1). Awareness can be further divided into awareness of the environment and awareness of self. Awareness of the environment can be defined as the conscious perception of one's environment through the sensory modalities (e.g. visual, auditory, somesthetic or olfactory perception) whereas awareness of self is a mental process that does not require the mediation of the senses and is not related to external stimuli for its presence (as shown by mind wandering, daydreaming, inner speech, mental imagery, etc.). Awareness of self also refers to the knowledge of our own social and cultural history as well as our family membership.

To be aware, we need to be awake but when awake, we are not necessarily aware. Consciousness depends on the interaction between the activity of the

cerebral cortex, the brainstem and thalamus. When one of these systems is disrupted, consciousness gets impaired. Thus, consciousness is not an all-or-nothing phenomenon but lies on a continuum of states (Wade 1996). The various states of consciousness include wakefulness, deep sleep and paradoxical sleep (dreaming sleep, i.e. rapid eye movement sleep, REM sleep), anesthesia, coma, vegetative state and the minimally conscious state (Fig. 2.1). The boundaries between these different states are not always sharp but often are progressive transitions.

But how do these disorders of consciousness (DOC) occur? As illustrated in Fig. 2.2, after an acute brain injury that could be of traumatic (i.e. motor vehicle accident, falling, etc.) or non-traumatic (i.e. stroke, anoxia, etc.) etiology, patients may lose consciousness and fall into a coma. In most cases where the damage is severe, patients die within a few days. From the moment the patients open their eyes, they move out of a coma and, if still unresponsive, evolve into a vegetative state. Typically, the vegetative patient (VS) gradually recovers awareness and enters a minimally conscious state (MCS). This is often followed by a period of transient post-traumatic amnesia where the patient remains confused and amnesic. In most cases, the patient recovers within a few weeks, but in some cases, they may remain in a state of no awareness or minimal consciousness for several months or even years or decades. Another exceptional condition the locked-in syndrome (LIS), where the patient awake from the coma fully conscious but is unable to move or communicate, except by eye movements.

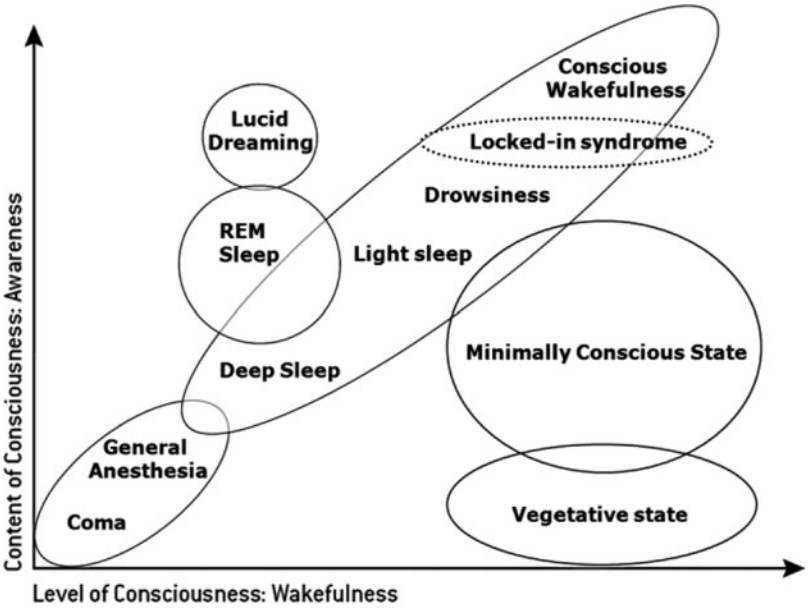


Fig. 2.1 Illustration of the two major components of consciousness: the level of consciousness (arousal or wakefulness) and the content of consciousness (awareness) in normal physiological states, where the level and the content of consciousness are generally positively correlated, and in pathological states or pharmacological coma (adapted from Laureys 2005)

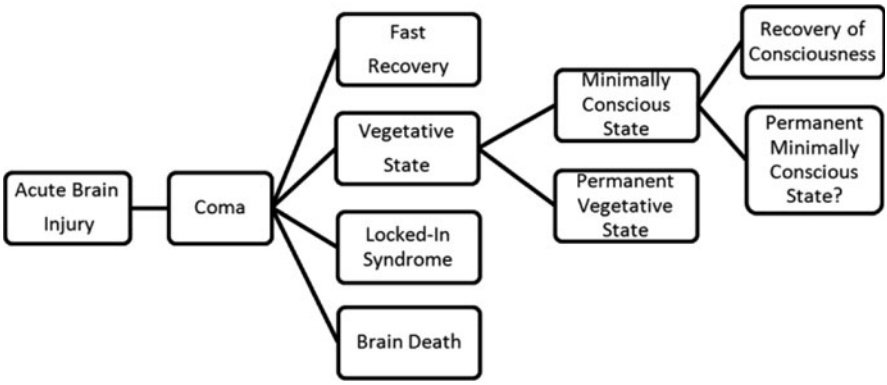


Fig. 2.2 Different conditions may follow acute brain injury. Classically, coma lasts for a couple of days, and once the patients open their eyes they evolve into a vegetative state. Then they may enter a minimally conscious state after showing some signs of consciousness, and eventually they recover full consciousness. In rare cases, a person may develop locked-in syndrome, a nearly complete paralysis of the body's voluntary motor responses

2.1.2 Clinical Entities

2.1.2.1 Brain Death

Brain death is characterized by the irreversible loss of all reflexes of the brainstem and the demonstration of continuing cessation of brain function and respiration in a persistently comatose patient (Laureys and Fins 2008). There should be an evident cause of coma, and confounding factors, such as hypothermia (low temperature), drugs intoxication, electrolyte, and endocrine disturbances should be excluded (Wijdicks 2001; Laureys 2005). Repeating the evaluation after 6 h is advised, but this time period is considered arbitrary (The Quality Standards Subcommittee of the American Academy of Neurology 1995). The absence of electrical brain activity by electroencephalogram (EEG) or the absence of cerebral blood flow may also serve as conformational tests (Laureys et al. 2004a).

2.1.2.2 Coma

Coma is a state of non-responsiveness in which the patients lie with eyes closed and cannot be awakened even when intensively stimulated (Plum and Posner 1983). Comatose patients are characterized by a lack of sleep–wake cycles (Teasdale and Jennett 1974) and they have neither verbal production nor response to command but can present reflexive responses to painful stimulation. In these patients, there is no awareness of self or of the environment. The autonomous functions such as breathing and thermoregulation are reduced and the patients require respiratory assistance.

Global brain metabolism (i.e. energy use) is also diminished by 50–70% of normal (Laureys 2005). Coma results from a diffuse cortical or white matter damage, or from a brainstem lesion (Vanhaudenhuyse et al. 2009). Coma must last at least 1 h to be distinguished from syncope, concussion, or other states of transient unconsciousness. The prognosis is often made within 3 days; if the etiology is traumatic, half of the patients who have no chance to recover will die during this short period (Schnakers et al. 2004). Prolonged comas are rare but can last 2–5 weeks and then progress to brain death, a vegetative state, or more rarely a locked-in syndrome.

2.1.2.3 Vegetative State

The vegetative state (VS), or newly called unresponsive wakefulness syndrom (Laureys et al, 2010), is defined by eyes opening, either spontaneously or after stimulation. The sleep–wake cycles are characterized by alternating phases of eye opening. The autonomous functions are preserved and breathing occurs usually without assistance. Patients in a vegetative state exhibit no intelligible verbalization, no voluntary response and no signs of awareness of self or the environment (The Multi-Society Task Force on PVS 1994). The vegetative patient is awake but not aware, which shows that both components of consciousness can be completely separated. If patients are still in a vegetative state a month after brain injury, they are said to be in a *persistent vegetative state*. If patients with a non-traumatic etiology remain in this state for more than 3 months, or more than 1 year for patients with a traumatic etiology, they are said to be in a *permanent vegetative state* (American Congress of Rehabilitation Medicine 1995; Jennett and Plum 1972). The term "persistent" refers to a chronic phase and implies an unfavorable prognosis about the possibility of improvement. This terminology confuses the diagnosis and the prognosis, which induces a risk that certain therapies, such as a transfer to a rehabilitation center, are denied to patients diagnosed as in a persistent vegetative state. Similarly, the term *permanent* implies near zero probability of recovery and can therefore give rise to decisions about the cessation of medication and nutrition. It is preferable to avoid using these two terms (often both abbreviated as PVS) and rather mention the duration and cause of the vegetative state.

The brainstem functions of a vegetative patient are preserved, but cortical (including frontal and parietal cortex) and thalamic injuries are present. Brain metabolism is diminished by 40–50% of normal values (Laureys et al. 2000a). The vegetative patient is able to perform a variety of movements, such as grinding teeth, blinking and moving eyes, swallowing, chewing, yawning, crying, smiling, grunting or groaning, but these are always reflexive movements and unrelated to the context. Motor behavior is reduced to a few stereotyped or reflexive movements and is inadequate compared to the intensity of the stimulation. Typical vegetative patients do not track with their eyes a moving object or their image in a mirror.

2.1.2.4 Minimally Conscious State

The minimally conscious state (MCS) (American Congress of Rehabilitation Medicine 1995; Giacino et al. 2002) is a more recently introduced entity and is characterized by primary and inconsistent signs of consciousness of self and the environment. Although patients are unable to communicate functionally, they can sometimes respond adequately to verbal commands and make understandable verbalizations. Emotional behaviors, such as smiles, laughter or tears may be observed. MCS patients may track a moving object, mirror or person (Giacino et al. 2002). Although these responses may be erratic, they must be reproducible in order to conclude that the action is intentional. These voluntary actions are quite distinct from reflexive movements if they are maintained for a sufficient period of time or repeated.

The overall cerebral metabolic activity is reduced by 20–40% (Laureys et al. 2004b). The autonomous functions are preserved and the thalamocortical and corticocortical connections are partly restored (Laureys et al. 2000b). The minimally conscious state may be transitory, chronic or permanent, such as the vegetative state.

2.1.2.5 Emergence of the Minimally Conscious State

Once patients are able to communicate in a functional way, they are said to have emerged from the minimally conscious state. They can therefore use multiple objects in an appropriate manner and their communication systems are adequate and consistent (Giacino et al. 2002). Because this entity is as recent as the minimally conscious state, validation and further research of other diagnostic criteria are still needed.

2.1.2.6 Locked-In Syndrome

Locked-in syndrome (LIS), also known as pseudocoma, is a complete paralysis of the body resulting from a lesion in the brainstem (American Congress of Rehabilitation Medicine 1995). Oral and gestural communications are impossible but patients are often able to blink and move the eyes. Despite the fact that the patients cannot move, their sensations are still intact and they are fully aware of their environment and themselves (Laureys et al. 2005a).

The only way for these patients to communicate with their environment is through eye movement and sometimes later also with the tip of a finger (Bauby 1997). Indeed, they generally recover some control of their fingers, toes or head. The LIS patient is able to answer questions by a simple code such as blinking once for “yes” and twice for “no”, or looking up for “yes” and down for “no”. Many means of communication have been developed to allow better communication, such as the use of the alphabet based on letter frequency used in English (i.e. E-T-A-O-I-

N-S-R-H-L-D-C-U-M-F-P-G-W-Y-B-V-K-X-J-Q-Z) where the patient blinks when the interlocutor pronounces the desired letter. Here it is necessary to begin over again for each letter in order to form words and sentences. The use of a brain computer interface has also recently become an option and allows a LIS survivor to control his or her environment, use a word processor, operate a telephone or access the Internet and use email (Gosseries et al. 2009).

Nearly 90% of LIS cases are of vascular etiology but they can also be traumatic. Cognitive functions are fully preserved if the lesion is only restricted to the brainstem. If additional cortical lesions are present, the cognitive functions associated with these cortical areas may be affected (Schnakers et al. 2008). Contrary to what we might expect, the quality of life reported by chronic LIS patients is not that much lower than the general population (Bruno 2011) and the demand for euthanasia, albeit existing, is infrequent (Bruno et al. 2008).

2.1.3 Prognosis

The prognosis for survival and recovery from coma, VS, MCS or LIS is still difficult to establish at the individual level. Certain factors, however, increase the chances of recovery. The young age of the patient, a traumatic etiology and the short duration of the state are linked with a better outcome (The Multi-Society Task Force on PVS 1994). Additionally, patients who are in a MCS for 1 month after brain injury have better chances of recovery than patients who are in a VS 1-month post-injury. Life expectancy of most vegetative patients varies between 2 and 5 years, a few patients stay more than 10 years in this state whereas the average survival time for LIS patients is about 6 years. Of notice is the fact that exceptionally some patients can recover even many years after their trauma. Indeed, the American Terry Wallis, who suffered a car accident in 1984, recovered from the minimally conscious state in 2003, 19 years later, he started talking (Wijdicks 2006). Similarly, a Polish man suffered a brain trauma in 1988 and was able to communicate only 19 years later, in 2007.

Clinical and paraclinical assessments can also be used to establish a prognosis, such as the evaluation of the brainstem reflexes, the sensory evoked potential (SEP), the cognitive auditory evoked potential (such as P300 and mismatch negativity, MMN), and the serum marker neuron-specific enolase (NSE). Some of these examinations are described in a later section.

2.2 Clinical Examination

In neurological rehabilitation, the distinction between a vegetative and a minimally conscious state is of great importance, because of the implications in terms of prognosis and treatment decisions, but also at the medico-legal and ethical level.

The main method – known as the gold standard – for detecting signs of consciousness is behavioral observation (Schnakers et al. 2004). The assessment of consciousness in DOC patients is essential from admission throughout hospital discharge in order to obtain information on their cognitive progress and to define appropriate care. Clinical evaluations are therefore used to assess the awareness of self and the environment of the patient. However, no technique is yet available to measure consciousness directly. We can identify its presence but it is much more difficult to prove its absence.

2.2.1 Misdiagnosis in Disorders of Consciousness

Although behavioral assessments are essential in evaluating consciousness, they are sometimes difficult to complete. A patient in a minimally conscious state can be diagnosed as being in a vegetative state, just as a LIS patient can be easily confused with a vegetative state. Indeed, voluntary movements may be wrongly interpreted as reflex movements and motor responses may be very limited due to a paralysis of all limbs (quadriplegia). Motor responses can also be quickly exhaustible and therefore not reproducible (Schnakers et al. 2004). The level of arousal can also fluctuate and patients may become drowsy or even fall asleep while evaluating them. All these boundaries lead to diagnostic errors. Studies have shown that 20–40% of patients diagnosed as vegetative showed signs of consciousness when assessed with sensitive and reliable standardized tools (consciousness scales) (Schnakers et al. 2006, Andrews et al. 1996, Childs and Mercer 1996, Schnakers et al. 2009).

The differential diagnosis requires repeated behavioral assessments by trained medical staff. The risk of misdiagnosis increases if the staff is unfamiliar with the clinical signs of these states. The controversy of some behaviors as reflecting consciousness or not just comes to add further perplexity. For example, blinking to visual threat should not be considered as a sign of consciousness (Vanhaudenhuyse et al. 2008a) whereas visual pursuit clearly should (Giacino et al. 2002). Moreover, the latter can be tested with different tools but it has been revealed that the best means for assessing visual pursuit is the use of a mirror which (by presenting the patient's own face) has the important ability to grab attention (Vanhaudenhuyse et al. 2008b). To avoid events of misdiagnosis, it is necessary that well-experienced personnel use standardized assessments, such as scales and individual testing, in order to objectify the clinical observations.

2.2.2 Consciousness Scales

Many standardized behavioral scales are used in the assessment of consciousness of brain injured patients: the Glasgow Coma Scale (GCS) (Teasdale and Jennett

1974), the Glasgow Liège Scale (Born 1988a), the Coma Recovery Scale-Revised (Giacino et al. 2004), the Full Outline of Unresponsiveness (Wijdicks et al. 2005), the Wessex Head Injury Matrix (Shiel et al. 2000), the Coma-Near Coma scale (Rappaport 2000), the Western Neuro-Sensory Stimulation Profile (Ansell and Keenan 1989), and the Sensory Modality Assessment and Rehabilitation Technique (Gill-Thwaites 1997) are among the most used. Some scales are an aid for diagnoses in the early hours of patients' admission in the intensive care unit (e.g. the GCS and FOUR) while others are rather used throughout the recovery (e.g. CRS-R). Here we review the scales that are used most frequently in clinical practice.

2.2.2.1 Glasgow Coma Scale and Glasgow Liège Scale

The Glasgow Coma Scale (GCS) is the scale of reference used internationally, due to its short and simple administration. It is mainly used in intensive care settings. The GCS measures eye, verbal and motor behaviors. However, the verbal response is impossible to assess in the case of intubation or tracheotomy (patients with artificial respiratory help making speech impossible). Additionally, there may be some concern as to what extent eye opening is sufficient for assessing brainstem function (Laureys et al. 2002a). The total score varies between 3 and 15. In acute stages, brain damage is described as serious if the score is less than or equal to 8 and moderate if the score is between 9 and 12 (Deuschl and Eisen 1999). The Glasgow Liège Scale (GLS) is an extended version of the GCS which includes the standardized evaluation of brainstem reflexes (Born 1988b).

2.2.2.2 Full Outline of Unresponsiveness

The Full Outline of Unresponsiveness (FOUR) is a more recent scale that has been proposed to replace the GCS as it detects more subtle neurological changes (Wijdicks et al. 2005). The scale is named after the number of subscales (eye, motor, brainstem reflexes and respiration) as well as after the maximum score that each subscale can take (four). The assessment takes only a few minutes to administer. It does not include a verbal response, and can therefore be used to assess artificially ventilated or intubated patients. The FOUR is particularly suitable for diagnosing vegetative state, locked-in syndrome and brain death. It also allows to differentiate between VS and MCS patients as it assesses visual pursuit, one of the first signs of recovery of consciousness (Giacino et al. 2002).

2.2.2.3 Coma Recovery Scale-Revised

The Coma Recovery Scale-Revised (CRS-R) also is a recent clinical tool that has been specifically developed to disentangle VS from MCS patients, but also MCS

patients from patients who recovered their ability to communicate functionally (Giacino et al. 2004). Indeed, it is the only scale to explicitly incorporate the diagnostic criteria of vegetative and minimally conscious state. It consists of six subscales: auditory, visual, motor and oromotor/verbal functions as well as communication and arousal. The 23 items are ordered according to their degree of complexity; the lowest item on each subscale represents reflexive activity while the highest item represents behaviors that are cognitively mediated. Scoring is based on the presence or absence of operationally defined behavioral responses to specific sensory stimuli (e.g. if the item of visual pursuit is present, the patient's state is diagnosed as minimally conscious). The brainstem reflexes are also measured but not scored. The assessment takes between 10 and 60 min, depending on the patient's responsiveness. In many research centers, the CRS-R is regarded as the gold standard for the behavioral assessment of severely brain injured patients. The scale has been translated and validated in several languages (Schnakers et al 2008) and is freely available (see http://www.comascience.org).

2.2.2.4 Wessex Head Injury Matrix

The objective of this scale is to create a transition between the assessment of coma in acute stages and the realization of neuropsychological tests that are applied much later. The evaluation is based on observations for presence or absence of behaviors. The WHIM has been designed to pick up minute indices demonstrating recovery and it covers a wide range of daily life functions. It assesses motor and cognitive skills, social interactions, the level of wakefulness and the auditivo-verbal, visual-motor and tactile modalities (Majerus and Van der Linden 2000). Compared to the CRS-R, this 62 item matrix assesses the patient without giving any diagnosis, since it does not incorporate the criteria of VS and MCS. It is more useful in assessing MCS patients who show minimal improvement, and in setting goals for rehabilitation from the outset of coma.

2.2.3 Individual Bedside Assessment

Another way to assess severely brain injured patients, which is complementary to the standardized scales, is a quantitative assessment based on the principles of single-subject experimental design. This method identifies whether a specific behavior of interest can be performed in response to command and whether the reliability of this behavior can change over time either spontaneously or in response to treatment (Whyte et al. 1999). The presence of command-following is crucial evidence of consciousness and facilitates differentiation between MCS and VS patients. The ability to follow a command is also important in the rehabilitation process because it means the patient can participate in therapies.

It can also be the starting point of communication. Indeed, specific movements can be used as a means of communication such as "make a thumbs up" for yes and "shake your head" for no.

Quantitative assessment can also lead to conclusions about a patient's visual function that are not readily apparent by clinical observation (Whyte and DiPasquale 1995). Attention deficits, blindness, gaze preference, monocular pathology and impairment in one or both visual fields can be observed objectively through this method by showing the patient a blank card or a photograph, either individually or at the same time, in both visual fields. Systematic visual orienting that involves visual discrimination is evidence of cortical function (i.e. if the patient looks at a picture more often than a blank card). The awareness of these deficits may help to avoid confounding the assessment of a patient's cognitive functions and can also help to adapt the therapy. For example, if a patient presents a left-sided neglect, the therapist should be positioned primarily on the right side to optimize patient's responsiveness.

2.3 Complementary Examination

Brain imaging and electrophysiology techniques are objective ways to investigate residual brain functions in disorders of consciousness. They may show the extent of brain damage for diagnostic, prognostic and therapeutic purposes and can also be used in experimental research. The imaging techniques can therefore lead to a better understanding of the behavioral clinical observations. To simplify, we present two main types of methods which are used for cognitive neuroimaging studies: metabolic or hemodynamic measurements (e.g. positron emission tomography, PET; functional magnetic resonance imaging, fMRI) and electrical measurements (e.g. electroencephalography, EEG; event related potentials, ERP). The PET technique can measure changes in the brain's metabolism using a radioactive tracer (labeled glucose) that is injected into the blood and is accumulated by active areas of the brain (using energy from the glucose). The fMRI indirectly measures regional increases in blood flow by analyzing the magnetic resonance properties of hemoglobin, which varies depending on the blood's oxygenation (energy use). These *functional* neuroimaging techniques should be distinguished from *structural* imaging such as X-ray CT or conventional MRI (offering imaging of the brain without telling anything about their functioning). Electrical measurements collect signals that are related to the intracellular electric current of the brain. PET and fMRI techniques have good spatial resolution but their temporal resolution is poor, whereas EEG methods have excellent temporal resolution but spatial resolution is relatively low and signals from deeper areas are difficult to identify (Laureys and Boly 2008).

2.3.1 Electroencephalography

Electroencephalography (EEG) records continuously and non-invasively the spontaneous electrical brain activity through electrodes placed on the scalp. The EEG well identifies the level of vigilance (Fang et al. 2005) and detects functional cerebral anomalies such as seizures. It can also be used to confirm the clinical diagnosis of brain death (Guérit et al. 2002). The utility of the EEG has been demonstrated to predict poor recovery of patients with brain anoxic and traumatic injury (Zandbergen et al. 1998). However, most of the EEG patterns are not specific (Young 2000) and do not allow reliable differentiation between conscious and unconscious brain processing. The interpretation of raw EEG signals also requires considerable expertise and training. More automated measures deriving from the EEG are therefore welcome, such as the EEG bispectral index measurements.

2.3.1.1 Bispectral Index

The bispectral index (BIS) measures the depth of sedation in anesthesia (Struys et al. 1998) and allows distinction between the different phases of normal sleep (Nieuwenhuijs et al. 2002). BIS values range between 0 and 100: when the subject is awake the values approach 100, whereas when the subject is under general anesthesia, values are around 40–50. BIS values also gradually increase when patients move out from coma to recovery (Schnakers et al. 2008a). However, BIS is a nonspecific measure of consciousness and does not systematically differentiate MCS from VS patients, even if it seems to show prognostic utility (Schnakers et al. 2005b).

2.3.1.2 Event-Related Potentials

The event-related potential (ERP) technique objectively examines sensory and cognitive functions at the patient's bedside by averaging the EEG activity according to the onset of a repeated stimulus (e.g. noise or visual flash). ERPs reveal the time course of information processing from low-level peripheral receptive structures to high-order associative cortices (Vanhaudenhuyse et al. 2008c). Short-latency ERPs, or exogenous ERP components (ranging from 0 to 100 ms), correspond to the passive (automatic) reception of external stimuli whereas cognitive ERPs, or endogenous ERP components (obtained after 100 ms), often reflect cognitive neuronal activity. The ERPs provide neurological markers, where the absence of early ERPs is a good predictor of a bad outcome (i.e. absence of primary cortical responses on somatosensory ERPs) and the presence of cognitive ERPs a good predictors of a favorable outcome (i.e. P300 and Mismatch Negativity responses) (Daltrozzo et al. 2007).

Short-Latency ERPs

Sensory evoked potentials (SEPs) are short-latency ERPs that are routinely used in intensive care. They measure the connection from the body to the brain (called the ascending pathways, which involve the spinal cord, the brainstem, and the primary sensory cortex). Practically, electrical stimulations are elicited from the wrist and the responses are recorded at the level of the nerves, spinal cord, brainstem and cortical levels. Bilateral absence of the cortical response (N20) among patients in coma, especially in anoxic patients who had a lack of oxygen in the brain, after for example cardiac arrest, is strongly associated with poor outcome, but preserved SEPs do not necessarily herald recovery (Cant et al. 1986; Laureys et al. 2005b).

Long-Latency Cognitive ERPs

Mismatch negativity (MMN) is a cognitive ERPs response elicited after approximately 100–200 ms by any change in a sequence of monotonous auditory stimuli in inattentive subjects (Naatanen and Alho 1997). It assesses the residual brain activity and more specifically the integrity of echoic memory, a memory that permits a sound to be remembered in the 2 or 3 s after it is heard. The presence of MMN has prognostic value in predicting recovery after coma (Kane et al. 1996; Fischer et al. 2004; Naccache et al. 2005; Qin et al. 2008).

The auditory evoked potentials P300 response is another ERP wave which is also elicited (around 300 ms after the stimulus) when subjects detect a rare and unpredictable target stimulus in a regular train of standard stimuli (Sutton et al. 1965). It assesses the integrity of acoustic and semantic discrimination. The presence of P300 and MMN is associated with a favorable clinical outcome but their absence does not necessarily imply a poor prognosis as these components can also be absent in some healthy controls, as well as in a significant number of patients who later recover consciousness (van der Stelt and van Boxtel 2008).

The P300 wave can also be observed in response to the patient's own name in VS and MCS patients, when they hear their own name in a sequence of unfamiliar names in a passive condition (Perrin et al. 2006). When asking patients to perform a cognitive task such as counting the number of times they hear their own name, the P300 to the own name stimuli increases (Schnakers et al. 2008b). This permits a demonstration that patients with apparently no behavioral sign of consciousness may be conscious (i.e. show command following) (Schnakers et al. 2009, p. 4588). The P300 ERP technique is also being used to permit EEG-based communication (i.e. in Brain Computer Interface technology) (Sellers et al. 2006), which could allow LIS patients to communicate through their electrical brain activity without moving a single muscle.

2.3.2 *Functional Neuroimaging*

2.3.2.1 Resting State

PET studies have shown that global cerebral metabolism during deep sleep and general anesthesia is diminished by about half of normal values (Maquet et al. 1997; Alkire et al. 1999). The brain metabolism of VS patients is also reduced by 50–60% (Laureys et al. 1999; Levy et al. 1987). However, when the patient has clinically recovered, brain metabolism does not always return back to normal (Fig. 2.3) (Laureys et al. 2000c).

Some brain regions appear to be more important than others for the emergence of consciousness. At rest, patients in a vegetative state show systematic impairment of metabolism in the frontoparietal network that includes polymodal associative cortices (bilateral prefrontal regions, Broca's area, parietotemporal and posterior parietal areas, and precuneus) (Laureys et al. 2006a).

These regions are essential in various functions that are necessary for consciousness, such as attention, memory, and language (Baars et al. 2003). Conscious perception is also linked to the functional connectivity between this frontoparietal network and deeper centers of the brain, such as the thalamus (Fig. 2.4). In vegetative patients, the long-distance connections between different cortical areas as well as between the cortex and the thalamus seem disconnected. The recovery of patients in a vegetative state is linked to the restoration of this frontoparietal network and its connections (Laureys et al. 2000b).

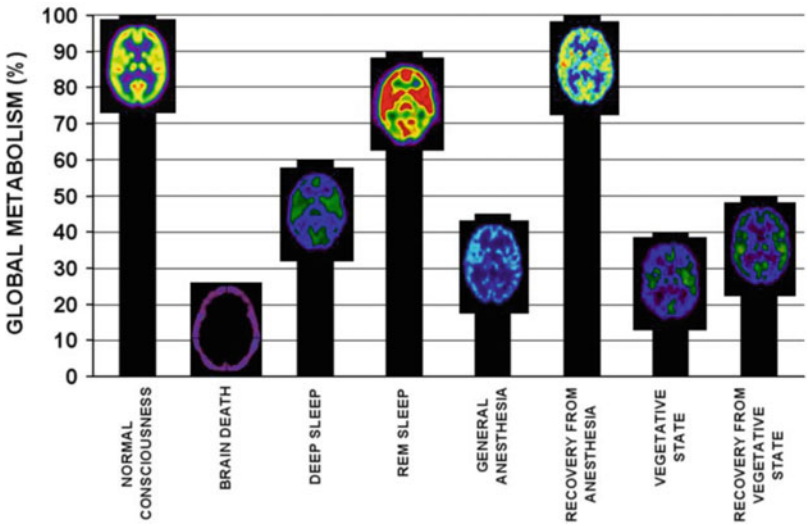


Fig. 2.3 Global cerebral metabolism in various states (adapted from Laureys et al. 2004a)

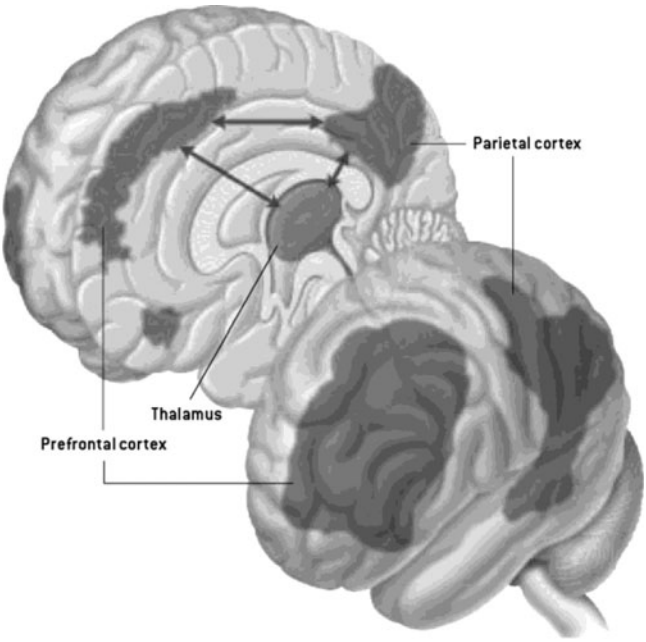


Fig. 2.4 Brain regions encompassing prefrontal and parietal multi-modal associative areas (known as the frontoparietal network) are crucial for consciousness. Conscious perception is also linked to the functional connectivity between this frontoparietal network and deeper centers of the brain such as the thalamus. The vegetative state is characterized by a metabolic dysfunction of this widespread cortical network shown in dark grey (adapted from Laureys 2007)

2.3.2.2 External Stimulation

Despite a massively reduced resting metabolism, primary cortices still seem to be activated during external stimulation in vegetative patients, whereas hierarchically higher-order multimodal association areas are not. When painful stimuli are administered to vegetative patients, only the brainstem, the thalamus and the primary somatosensory cortex are activated, and the latter is isolated and disconnected from the other brain areas, in particular the frontoparietal network (Boly et al. 2005; Laureys et al. 2002b). These findings support the idea that patients in a vegetative state do not consciously perceive pain as do healthy people. In contrast to VS, MCS patients, similar to control subjects, show activation of the complete pain matrix (thalamus, primary and secondary somatosensory, frontoparietal, and anterior cingulate cortices) and show a preserved functional connectivity between these areas (Boly et al. 2008). These results provide evidence for a preserved conscious pain perception capacity in MCS patients, strongly suggesting that these patients should receive pain treatment when needed.

Similarly, in response to auditory stimuli, brain activity in vegetative patients is limited to the primary auditory cortex while polymodal areas of higher order do

not become active and remain functionally disconnected (Boly et al. 2004; Laureys et al. 2000d). This primary brain activation does not seem enough to lead to conscious perception and memory formation. In contrast, patients in a minimally conscious state activate higher-order cortical areas. More specifically, a recent study showed a selective impairment in backward connectivity from frontal to temporal cortices in vegetative patients whereas minimally conscious patients present a similar pattern to healthy subjects with preserved feedforward and top-down processes (Boly et al. 2011) Auditory stimuli with emotional content, such as baby cries or the patient's own name, induce even more extensive brain activation than sounds without meaning (Fig. 2.5) (Laureys et al. 2004b; Boly et al. 2005). This implies that content is important when talking to patients in a minimally conscious state.

Similarly, in response to presentation of the patient's own name uttered by a familiar voice, the primary auditory cortices of five VS patients were activated, but none of these patients recovered. In contrast, two other VS patients showed atypical activation of both primary cortex and higher-level associative cortex, and they improved clinically to MCS 3 months after their scan (Di et al. 2007). Another fMRI study showed that MCS patients demonstrated similar responses to healthy volunteers when listening to passive language with personalized narratives. However, when the narratives were presented as a time-reversed signal (without linguistic content) MCS patients demonstrated markedly reduced responses, suggesting again reduced engagement for linguistically meaningless stimuli (Schiff et al. 2005).

Another fMRI study based on mental imagery tasks has been proposed to identify signs of consciousness in non-communicative patients (Boly et al. 2007). Despite the clinical diagnosis of vegetative state, a 23-year-old girl who suffered a traumatic brain injury 5 months earlier showed signs of consciousness only detectable on fMRI (Owen et al. 2006). She was asked to imagine herself playing tennis and walking

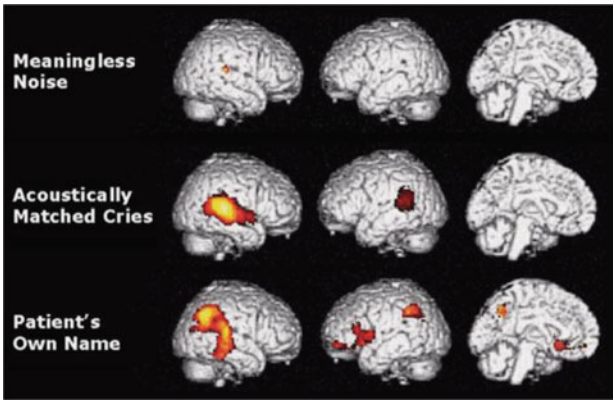


Fig. 2.5 Brain activations during presentation of noise, baby cries, and the patient's own name. Stimuli with emotional valence (baby's cries and names) induce a much more widespread activation than does meaningless noise in the minimally conscious state (taken from Laureys et al. 2004)

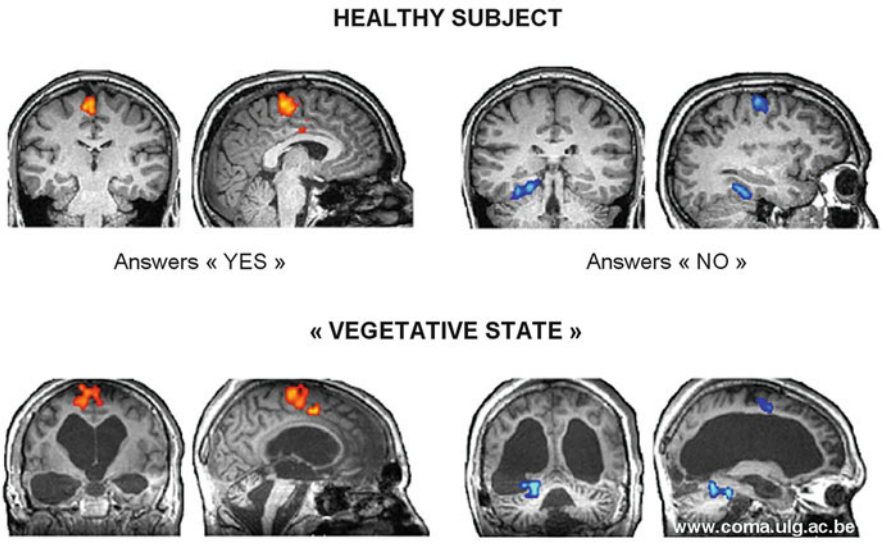


Fig. 2.6 A patient (top two images) who was clinically diagnosed as vegetative showed similar brain activity to a healthy subject (bottom two images) when asked to imaging playing tennis (*left*) or visiting her own house (*right*). A few months after the study, the patient recovered consciousness (taken from Owen et al. 2006)

through her house. The results showed brain activation similar to that of the control subjects for both tasks (Fig. 2.6). This study shows clear evidence of awareness and command-following in the absence of voluntary motor responsiveness. The patient evolved into MCS several weeks later and she was probably in a stage of transition from vegetative to recovery of consciousness at the time of assessment. Finally, another study recently showed that it has been possible for a vegetative patient to communicate through the fMRI. He could answer questions by imaging playing tennis when he wanted to say "yes" and imaging moving into his house when he wanted to respond "no" (Monti and Vanhaudenhuyse et al, 2010).

2.4 Treatment

There is currently no effective standardized treatment for DOC patients. Most of the studies have been conducted under suboptimal settings with methodological and conceptual problems, with the consequence that no strong evidence-based recommendations can be made. However, uncontrolled studies indicate that some rehabilitative procedures can promote the recovery of consciousness, especially in MCS patients. These interventions can be divided into pharmacological and non-pharmacological treatments.

2.4.1 Pharmacologic Treatment

The effect of pharmacological agents on recovery in chronic disorders of consciousness still remains unsatisfactory (Laureys et al. 2006b; Demertzi et al. 2008). Several therapeutic trials have been conducted with post-comatose patients and have led to a marked improvement in their level of consciousness. Zolpidem is a drug originally used in the treatment of insomnia that has occasionally the opposite effect in brain damaged patients. A recent study showed that on 15 patients, only one demonstrated a clinically significant response after the administration of the medication, suggesting a response rate to zolpidem around 7% (Whyte et al. 2009). The effect of Zolpidem was first reported after its use in a 23-year-old man who had been in a vegetative state for more than 3 years following a motor vehicle accident. The patient regained consciousness 15 min after being administered the drug and was able to greet his mother for the first time in 3 years. He was able to sigh, to talk and to communicate with his family (Clauss et al. 2000). But after the effects of the drug wore off, he relapsed, returning to his previous state. Zolpidem has therefore only a temporary effect and lasts for a maximum of a few hours. Temporary improvements have since been observed in stroke and near drowning patients (Clauss and Nel 2004), anoxic brain injury (Cohen and Duong 2008), vegetative (Clauss and Nel 2006) and minimally conscious states (Brefel-Courbon et al. 2007; Shames and Ring 2008). The results varied from a regain of consciousness to an enhancement of motor, verbal and cognitive functions, as well as gestural interaction and arousal. The exact underlying mechanism of the effect of Zolpidem remains unclear (Clauss et al. 2004).

Amantadine is another drug that produces similar effects on VS and MCS patients but its effects last longer (Whyte et al. 2005; Zafonte et al. 2000). It is a dopaminergic agent (also acting on NMDA receptors) initially used against the flu and in the treatment of Parkinson's disease. A recent study involving a chronic anoxic MCS patient showed cognitive improvement after 3 weeks of Amantadine treatment, such as reproducible movement to command (i.e. touching a ball with the feet) and consistent automatic motor responses (i.e. mouth opening when a spoon is approaching). These improvements were associated with an increase in fronto-parietal cortical metabolism which is considered important in consciousness (Schnakers et al. 2008c).

Other pharmacological agents that have been reported as inducing functional recovery are Levodopa, Bromocriptine (Passler and Riggs 2001) Apomorphine (Fridman et al. 2010), and Baclofen (Taira and Hori 2007). Large scale studies on the efficacy of these drugs are still warranted. More specifically, cohort placebo-controlled randomized trials and blinded within-subject crossover designs are needed before reaching any definite conclusions concerning the efficacy of the pharmacological treatment of DOCs.

2.4.2 Non-pharmacological Treatment

Deep brain stimulation (DBS) has been proposed as a strategy to improve the functional level of chronic non-communicative patients. This technique consists of implanting an electrode in the brain (more specifically in this case in the thalamus) in order to reactivate a widespread cerebral connectivity mechanism that supports communication and goal-directed behavior. Bilateral DBS of the central thalamus has been performed in a 38-year-old patient who remained in a MCS for 6 years following a traumatic brain injury (Schiff et al. 2007). The electrodes were placed in the intralaminar thalamic nuclei. It has been shown that these thalamic nuclei restore cortical connectivity in the recovery of consciousness after VS (Laureys 2000b, p. 2913). Before applying DBS, the MCS patient failed to recover consistent command following and remained in a non-verbal state without any sign of functional communication. His fMRI, however, showed the preservation of a bihemispheric large-scale cerebral language network, which demonstrates that further recovery was possible (Schiff et al. 2005). During periods in which DBS was on (as compared to periods in which it was off), levels of arousal, motor control and interactive behavior increased considerably. The patient was able to respond consistently to commands and produced intelligible verbalization. The DBS technique can therefore promote a significant functional recovery from severe traumatic brain injury. Nevertheless, replicas of these findings are still needed to validate the technique.

Other non-pharmacologic and non-invasive interventions are the multimodal sensory stimulation techniques which provide frequent sensory input to all five senses in the hope that it will enhance synaptic reinnervation and accelerate neurological recovery (Demertzi et al. 2008; Tolle and Reimer 2003). Sensory stimulation is also intended to prevent sensory deprivation and facilitates coherence between the brain and the body. Sensory regulation is a variant of sensory stimulation that facilitates information processing by adjusting the time exposure and the complexity of the stimuli according to the level of the patient's capacity (Wood et al. 1992). The stimulation sessions are alternated with resting periods in order to increase the ability of the patient to respond during stimulation sessions. Finally, physical and occupational therapy are usually used in rehabilitation centers to prevent complications and enhance recovery. There is uncontrolled evidence that early and increased intervention leads to better outcomes (Oh and Seo 2003; Shiel et al. 2001). The beneficial effects of all these techniques are still debated and are not yet based on evidence.

2.5 Ethical Issues

DOC patients, especially patients in vegetative state, present important ethical and moral issues (Demertzi et al in press). In many countries, it is legally permissible to withdraw life-sustaining treatment once the patient is diagnosed as being in a

permanent VS (i.e. with no hope of recovery), if such withdrawal seems likely to be what the patient would have wanted (Jennett 2005). It is therefore recommended to make an advance directive concerning personal wishes in the event of vegetative survival that could legitimately be used by the doctor to withdraw or to sustain the treatment (Demertzi et al 2011).

Three cases have generated considerable debate, positioning pro-life advocates against those defending the right to die with dignity. American Karen Ann Quinlan suffered a cardio-pulmonary arrest in 1975 and became vegetative. Her parents signed the authorization to disconnect the respirator, but the hospital authorities refused because the parents did not have legal custody. A judicial process began and a year later the court gave legal custody to the parents. Karen was disconnected but, against all odds, she continued breathing by herself. She survived in this vegetative state for 9 years until her death in 1985 (Dundon 1978). The case of the American Terri Schiavo is similar but here the parents wished to keep her alive against the wishes of her husband and despite the advice of doctors. After suffering a respiratory insufficiency in 1990, Terri was considered as being in a permanent vegetative state but this diagnosis was criticized by the parents still hoping for a recovery (Cochrane 2006). The Supreme Court of the United States finally rejected the request of her parents to keep her alive and she died in 2005, 13 days after the disconnection of her feeding tube. The most recent case involved the Italian Eluana Englaro, who was left in a vegetative state after a motor vehicle accident in 1992. Her father requested shortly after the accident to have her feeding tube removed but the authorities refused his request. He received the authorization only 17 years later. She finally died in February 2009.

It is also ethically controversial for some whether or not non-communicative patients can be included in clinical trials, as they are unable to provide their agreement. Informed consent is therefore requested from the patient's legal surrogate. The medical community is redefining an ethical framework in order to balance protection for post-comatose patients against the facilitation of research and medical progress (Fins 2003; Fins et al. 2008).

2.6 Conclusion

Defining consciousness as having two components (arousal and awareness) helps us also define the corresponding clinical entities. Coma means lack of consciousness (unarousable unawareness), whereas in the vegetative state arousal is preserved but awareness is absent (arousable unawareness). In the minimally conscious state, arousal is also present but with fluctuating and minimal signs of awareness. Locked-in syndrome has to be differentiated from those disorders of consciousness, as consciousness is intact but voluntary motor control is completely impaired (except for eye movements). In clinical practice, although the Glasgow Coma Scale remains the gold standard for the assessment of comatose patients, the Coma Recovery Scale-Revised is more appropriate in differentiating between

vegetative and minimally conscious or locked-in patients. Misdiagnosis is still too frequent in clinical practice despite the introduction of diagnostic criteria. Conscious patients can indeed be diagnosed as vegetative if they have unnoticed paralysis or if voluntary movements are erroneously interpreted as reflexes. Family members of LIS patients are often the first to realize that the patient is conscious (Laureys et al. 2003; Leon-Carrion et al. 2002). Standardized behavioral scales and quantitative individual assessments should therefore be employed repetitively in the clinical routine by trained medical staff, in order to minimize the risk of erroneous diagnosis.

Technological advances in neuroimaging allow us to increase our understanding of the human brain and this knowledge can be exploited in order to develop new diagnostic, prognostic and therapeutic approaches (Laureys and Boly 2008). Studies have shown that the vegetative state is characterized by a functional cortical disconnection syndrome. Only primary cortex can be activated and is disconnected from the higher-order frontoparietal network. In the minimally conscious state, however, the latter areas can be activated especially by emotionally meaningful or noxious stimuli. It has also been shown that neuronal plasticity (e.g. axonal regrowth) may exist, sometimes many months to years after the brain trauma, and this could promote the recovery of consciousness in MCS patients (Schiff et al. 2005; Voss et al. 2006).

DOC patients have rather limited therapeutic options. Basic therapies include life-sustaining therapy (i.e. artificial nutrition and hydration) as well as physical and occupational therapies that are used to prevent complications and enhance recovery (the latter awaits controlled trials). Pharmacologic trials (with Amantadine and Zolpidem) have shown behavioral improvements in some uncontrolled case reports or series of brain injured patients. Deep brain stimulation and multisensory stimulations also showed some positive results but are clearly still in the research domain. Nowadays, therapeutic management lacks large-scale double-blind randomized placebo controlled trials. Much more research and methodical validation are required before accepting or rejecting specific treatments.

Advanced communication techniques based on mental imagery and on cognitive event-related potentials using active paradigms are also currently being investigated. Indeed, brain computer interface (BCI) devices allow brain signals to control external devices without requiring any muscular activity. For example, mental imagery and measurement of the salivary pH can permit a LIS patient to communicate: to say “yes”, the patient had to imagine a lemon, which increases salivary pH, whereas to say “no”, the patient had to imagine milk, which decreases pH (Wilhelm et al. 2006; Vanhaudenhuyse et al. 2007). Also, it is expected that BCI techniques will be used clinically as a diagnostic tool for differentiating between conscious and unconscious patients (Kubler and Kotchoubey 2007, Sorger 2009), as we have previously seen with the fMRI tennis and spatial mental imagery paradigms.

Neuroimaging studies are moving from the research field to the clinical application of these techniques currently being validated by multi-centric cohort studies. These paraclinical examinations are providing additional information, unavailable

through bedside clinical assessments, which is being used to better understand the patient's diagnosis and prognosis. It can be predicted that in the near future, multimodal approaches combining bedside examination, electrophysiology and functional imaging techniques will be routinely employed to assess and treat these challenging patients with disorders of consciousness.

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Comment évaluer la conscience chez des patients sévèrement cérébrolésés ?

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1. Introduction

Grâce au perfectionnement des techniques de réanimation, de plus en plus de personnes survivent à un accident cérébral grave, qu'il soit d'origine traumatique ou anoxique. Alors que la majorité des patients récupèrent de leur coma dans les jours qui suivent l'accident, certains perdent définitivement toute fonction cérébrale (mort cérébrale), tandis que d'autres passent par différents stades, tels que le syndrome d'éveil non-répondant/état végétatif, l'état de conscience minimale ou le *locked-in* syndrome, avant de récupérer partiellement ou totalement un état de conscience normale. L'évaluation comportementale est actuellement l'outil principal pour établir un diagnostic d'état de conscience altérée chez ces patients. Cependant, la pratique clinique démontre que détecter des signes de conscience au chevet des patients reste difficile. Une expertise dans ce domaine, ainsi que la nécessité d'inclure d'autres outils objectifs d'évaluation de la conscience revêt d'une importance majeure, et ce, afin d'affiner le diagnostic et d'optimaliser la prise en charge des patients.

2. Définition clinique de la conscience

Avant de définir les états de conscience altérée typiquement rencontrés après un coma, il nous semble important de définir le terme *conscience*. La conscience

a deux composantes[1] : l'éveil (*arousal*) et le contenu de la conscience (*awareness*) (Figure 1, p. 15).

L'éveil est caractérisé par une ouverture des yeux spontanée ou induite par des stimulations (auditives ou tactiles), un tonus musculaire et un électroencéphalogramme indiquant des fréquences rapides[2]. La modulation de l'état d'éveil dépend du tronc cérébral et de ses projections thalamiques et corticales[3].

La deuxième composante, le contenu de la conscience, représente la somme de toutes les fonctions centralisées dans le cortex cérébral, c'est-à-dire toutes les fonctions affectives et cognitives[4]. En général, l'individu doit être éveillé pour être conscient. Dans les états physiologiques non pathologiques, tels que les différents stades de sommeil, l'éveil et la conscience sont positivement corrélés (exception faite du sommeil paradoxal – Figure 1, p. 15). Les patients en coma ou sous anesthésie générale ne sont ni éveillés, ni conscients. D'autres états pathologiques, tels que l'état végétatif/non répondant, le mutisme akinétique, les crises d'épilepsie et l'état de conscience minimale sont caractérisés par une dissociation entre l'éveil et la conscience. Enfin, les patients en *locked-in* syndrome présentent un niveau d'éveil et de conscience similaire à celui observé chez les personnes dont la conscience est préservée.

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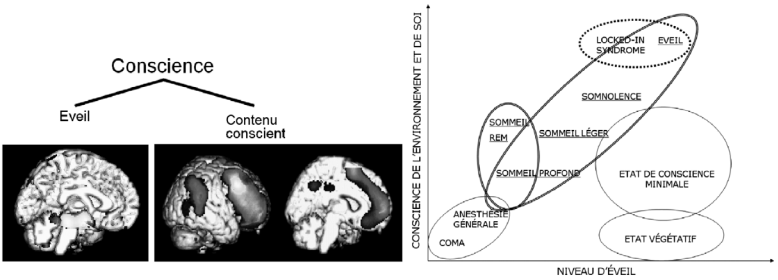
1 A. Zeman, « Consciousness », *Brain*, 2001, 124(7), pp. 1263-1289.

2 A. Damasio et K. Meyer, « Consciousness : An overview of the phenomenon and of its possible neural basis », *in The neurology of consciousness : Cognitive neuroscience and neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, UK, Academic Press, 2009, pp. 3-14.

3 B.A. Vogt et S. Laureys, « Posterior cingulate, precuneal and retrosplenial cortices : cytology and components of the neural network correlates of consciousness », *Prog Brain Res*, 2005, 150, pp. 205-217.

4 J. Posner, C. Saper, N. Schiff et F. Plum, *Plum and Posner's diagnosis of stupor and coma*, New York, Oxford University Press, 2007.

Figure 1



L'image de gauche représente les corrélats neuronaux des 2 composantes de la conscience : l'éveil (activation de la formation réticulée) et le contenu de la conscience (activation du réseau fronto-pariétal). L'image de droite illustre les différents états de conscience en fonction de l'éveil et de la conscience externe et interne[5].

Le contenu de la conscience, tel que décrit plus haut, peut également être divisée en deux sous composantes : la conscience de l'environnement et la conscience de soi[5]. La conscience de soi est associée aux notions d'identité, d'autobiographie et de personnalité. Cette dernière existe grâce à la conscience de l'environnement qui permet d'acquérir et d'assimiler des expériences par l'intermédiaire des interactions avec l'environnement extérieur. En l'absence de communication, comme c'est le cas chez les patients en état de conscience altérée post-coma, nous sommes limités à l'observation des comportements liés à la conscience de l'environnement.

3. Les états de conscience altérée

Il existe différents états de conscience altérée qui se distinguent par la présence et/ou l'absence des deux composantes de la conscience que nous avons

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5 W. James, *The Principles of Psychology,* New York, Macmillan Publishing Co Inc,1890 ; A. Vanhaudenhuyse, A. Demertzi, M. Schabus, Q. Noirhomme, S. Bredart, M. Boly, C. Phillips, A. Soddu, A. Luxen, G. Moonen et S. Laureys, « Two Distinct Neuronal Networks Mediate the Awareness of Environment and of Self », *J Cogn Neurosci*, 2010a.

6 Adapté de A. Vanhaudenhuyse, C. Schnakers, M. Boly, F. Perrin, S. Bredart et S. Laureys, « Detecting consciousness in minimally conscious patients », *Réanimation*, 2007b, 16, pp. 527-532 ; M. Boly, C. Phillips, L. Tshibanda, A. Vanhaudenhuyse, M. Schabus, T.T. Dang-Vu, G. Moonen, R. Hustinx, P. Maquet et S. Laureys, « Intrinsic brain activity in altered states of consciousness : how conscious is the default mode of brain function ? », *Ann N Y Acad Sci*, 2008b, 1129, pp. 119-129.

évoquées précédemment, l'éveil et la perception consciente (Figure 1, p. 15). Classiquement, après une lésion cérébrale aiguë qui peut être d'origine traumatique (accident de roulage, chute, etc.) ou non traumatique (accident vasculaire cérébral, arrêt cardiaque, etc.), le patient perd connaissance et tombe dans le coma. Lorsque les lésions sont très importantes, le plus souvent, le patient décède dans les jours qui suivent. Plus rares sont les patients qui décèderont après un coma de plusieurs semaines. À partir du moment où le patient ouvre les yeux, il sort du coma et évolue vers un état végétatif/non répondant. Le patient reprend ensuite graduellement une activité consciente qui se poursuit souvent par une période d'amnésie post-traumatique transitoire au cours de laquelle il reste confus. Dans la majorité des cas, le patient récupère en quelques semaines et peut ensuite entreprendre une prise en charge rééducative. Mais dans certains cas, le patient reste dans un état de non-conscience ou de conscience minimale pendant plusieurs mois, voire plusieurs années ou décennies.

3.1. *Mort cérébrale*

La mort cérébrale décrit la mort selon des critères neurologiques. Les premiers patients dits en *mort cérébrale* sont apparus dans les années 1950. En effet, ces patients pouvaient être maintenus en vie à l'aide de nouvelles techniques de réanimation et de ventilation artificielle. La définition officielle de la mort cérébrale fut proposée par *The Harvard Medical School Ad Hoc Committee* (1968) qui précisa qu'un patient ne pouvait être diagnostiqué en mort cérébrale que s'il démontrait une cessation permanente et irréversible de toutes fonctions neurologiques. Quelques années plus tard, cette définition est affinée par Bernat[7] qui propose qu'un patient ne soit déclaré en mort cérébrale que lorsque toutes ses fonctions cérébrales ont cessé de fonctionner de manière permanente, indépendamment d'une ventilation et d'une circulation artificielles (Tableau 1, p. 28). Le diagnostic de mort cérébrale est donc basé sur la perte définitive de tous les réflexes du tronc cérébral (réflexes pupillaires, cornéens, oculo-vestibulaires, nauséeux et de toux), une absence continue de respiration mise en évidence grâce à un test d'apnée, un coma démontré comme étant profond et non réactif à des stimuli nociceptifs, et l'exclusion de facteurs confondants tels que des troubles hypothermiques, médicamenteux,

[7] J.L. Bernat, *Brain Death. The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 151-162.

électrolytes et endocriniens[8]. Des mouvements très ralentis et générés par une activité spinale résiduelle peuvent toutefois être observés chez un tiers des patients en mort cérébrale : extension réflexe des doigts, flexion réflexe des orteils, signe de Lazare et myokimies faciales[9]. Par ailleurs, les patients en mort cérébrale ne présentent jamais d'expression faciale ni de vocalisation[10]. Une réévaluation dans les six à vingt-quatre heures est conseillée afin de confirmer le diagnostic[11]). Des examens par électroencéphalographie (EEG), potentiels évoqués, angiographie, doppler transcrânien ou scintigraphie cérébrale sont nécessaires afin de confirmer les tests neurophysiologiques. Les causes principales de mort cérébrale sont un traumatisme crânien, une hémorragie sous-arachnoïdienne anévrismale, une hémorragie intracrânienne, un accident vasculaire cérébral ischémique, une encéphalopathie hypoxique-ischémique, ou encore une nécrose hépatique fulminante[12]. L'EEG d'un patient en mort cérébrale est caractérisé par une absence d'activité électro-corticale. La neuroimagerie fonctionnelle démontre, quant à elle, une absence totale de fonctions neuronales dans l'entièreté du cerveau[13]. Au niveau du pronostic, des études ont démontré qu'aucun patient déclaré en mort cérébrale n'avait jamais récupéré et que si les réflexes du tronc cérébral ne réapparaissaient pas dans l'heure suivant l'accident, aucune récupération n'était à espérer.

La mort cérébrale est étroitement liée à la problématique du don d'organe. En effet, le patient doit être déclaré en mort cérébrale avant que la procédure

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8 S. Laureys, « Science and society : death, unconsciousness and the brain », *Nat Rev Neurosci*, 2005, 6(11), pp. 899-909 ; J.L. Bernat, *Brain Death. The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 151-162.

9 G. Saposnik, J.A. Bueri, J. Maurino, R. Saizar et N.S.Garretto, « Spontaneous and reflex movements in brain death », *Neurology*, 2000, 54(1), pp. 221-223 ; G. Saposnik, J. Maurino, R. Saizar et J.A. Bueri, « Spontaneous and reflex movements in 107 patients with brain death », *Am J Med*, 2005, 118(3), pp. 311-314.

10 S. Laureys, « Science and society : death, unconsciousness and the brain », *Nat Rev Neurosci*, 2005, 6(11), pp. 899-909.

11 The Quality Standards Subcommittee of the American Academy of Neurology, « Practice parameters : assessment and management of patients in the persistent vegetative state (summary statement) », *Neurology*, 1995, 45(5), pp. 1015-1018 ; E.F. Wijdicks, « Brain death worldwide : accepted fact but no global consensus in diagnostic criteria », *Neurology*, 2002, 58(1), pp. 20-25 ; J. Posner, C. Saper, N. Schiff et F. Plum, *Plum and Posner's diagnosis of stupor and coma*, New York, Oxford University Press, 2007.

12 J. Posner, C. Saper, N. Schiff et F. Plum, *Plum and Posner's diagnosis of stupor and coma*, New York, Oxford University Press, 2007.

13 Pour une revue, voy. S. Laureys, A.M. Owen et N.D. Schiff, « Brain function in coma, vegetative state, and related disorders », *Lancet Neurol*, 2004b, 3(9), pp. 537-546.

de don d'organes ne puisse être autorisée. Éthiquement, les chirurgiens chargés de la transplantation d'organes sont exclus de la procédure diagnostique du patient. Le protocole pour « le don d'organe après une mort cardiaque »[14] permet également de prélever des organes chez des patients comateux sans espoir de récupération, maintenus en respiration ventilée aux soins intensifs, mais n'étant pas en mort cérébrale. Dans ce cas, et si le patient a préalablement donné son accord, une procédure d'arrêt de toute thérapie (ventilation contrôlée) est entamée. Dans ces cas particuliers, des tests répétés sont exigés afin de s'assurer que le patient n'a réellement aucune chance de récupérer de son coma[15].

3.2. *Coma*

Le coma est caractérisé par une absence complète d'éveil et donc une absence d'ouverture des yeux (même lors de stimulations intensives – Tableau 1, p. x), causée par une lésion dans le système activateur réticulaire, ainsi qu'une absence de conscience de soi et de l'environnement[16]. Afin de distinguer le coma d'une syncope, d'une commotion ou d'un autre état de perte de conscience transitoire, le coma doit durer au moins une heure. Il peut se prolonger de quelques jours à quelques semaines, ce qui est souvent le cas pour les comas pharmacologiques. Les patients évolueront progressivement dans les deux à quatre semaines en passant par différents stades tels que l'état végétatif/non répondant, l'état de conscience minimale ou le *locked-in* syndrome (Figure 1, p. 15). Des lésions bi-hémisphériques diffuses du cortex ou de la matière blanche, ou des lésions du tronc cérébral affectant particulièrement les systèmes d'éveil réticulaire sous-corticaux peuvent expliquer un coma. Différents facteurs tels que l'étiologie, l'état général de santé du patient, l'âge ou les signes cliniques influent la prise en charge et le pronostic de récupération du coma. Après trois jours d'observation, certains critères sont reconnus comme

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14 or "DCD – donation after cardiac death", University of Pittsburgh Medical Center policy and procedure manual 1993.

15 J.L. Bernat, A.M. D'Alessandro, F.K. Port, T.P. Bleck, S.O. Heard, J. Medina, S.H. Rosenbaum, M.A. Devita, R.S. Gaston, R.M. Merion, M.L. Barr, W.H. Marks, H. Nathan, K. O'Connor, D.L. Rudow, A.B. Leichtman, P. Schwab, N. L. Ascher, R.A. Metzger, V. Mc Bride, W. Graham, D. Wagner, J. Warren et F.L. Delmonico, « Report of a National Conference on Donation after cardiac death », *Am J Transplant*, 2006, 6(2), pp. 281-291.

16 J. Posner, C. Saper, N. Schiff et F. Plum, *Plum and Posner's diagnosis of stupor and coma*, New York, Oxford University Press, 2007.

étant de très mauvais pronostic : une absence des réflexes pupillaires et/ou cornéens, une absence de réponses motrices ou des réponses stéréotypées lors de stimulations nociceptives, un EEG isoélectrique, une absence bilatérale de réponses corticales aux potentiels évoqués somesthésiques (PES), et un taux important du marqueur biochimique d'énolase neurospécifique pour les étiologies anoxiques (NSE)[17]. L'ensemble des travaux ayant étudiés le pronostic des patients en coma après un accident traumatique démontre que des réponses motrices anormales aux stimuli nociceptifs (flexion/extension stéréotypée), l'âge (> 60 ans), l'absence de réflexes pupillaires, une hypotension ou une hypoxie, un CT scan anormal (compression des citernes basales ou dépassement de la ligne médiale), la durée du coma, l'absence bilatérale de PES et un taux élevé d'acide protéique fibrillaire glial et de S100B (protéine acide spécifique des cellules gliales) sont autant de facteurs corrélés à un mauvais pronostic[18]. Quant aux patients d'étiologie non-traumatique, les réponses motrices anormales aux stimuli nociceptifs (flexion/extension stéréotypée), l'absence des réflexes du tronc cérébral (réflexes pupillaires, cornéens et oculovestibulaires), la durée du coma (> 6 heures), un taux élevé de S100b, ainsi qu'une cause ischémique-vasculaire ou hémorragique sont également prédictifs d'un mauvais pronostic[19]. Par ailleurs, le pronostic des patients dont l'étiologie est traumatique est significativement meilleur que celui des patients dont l'étiologie est anoxique[20]. Le taux de mortalité d'un patient en coma varie de 40 à 88 % selon que l'étiologie soit anoxique ou traumatique.

3.3. *État végétatif – syndrome d'éveil non répondant*

Après quelques jours à quelques semaines, le patient peut évoluer et ouvrir les yeux. Quand cette récupération du cycle veille-sommeil s'opère, sans être accompagnée d'aucun signe de conscience, le patient est diagnostiqué comme étant en état végétatif (Tableau 1, p. 28). Jennet et Plum[21] ont choisi le terme *végétatif* tel qu'il est décrit dans le *Oxford English Dictionary* : *to be vegetate – être en vie physiquement sans pouvoir jouir d'une activité intellectuelle ou*

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17 S. Laureys, M. Boly, G. Moonen et P. Maquet, « Arousal and awareness in coma and post-comatose states », *New Encyclopedia of Neuroscience*, L. Squire, Eslevier, 2008.

18 J. Posner, C. Saper, N. Schiff et F. Plum, *Plum and Posner's diagnosis of stupor and coma*, New York, Oxford University Press, 2007.

19 *Ibid.*

20 *Ibid.*

21 B. Jennett, F. Plum, *Persistent vegetative state after brain damage*, RN 35(10) : ICU1-4, 1972.

d'interactions sociales ; vegetative – organisme capable de croître et de se développer, mais dépourvu de sensation et de pensée. Récemment, le groupe *The European Task Force on Disorders of Consciousness* a proposé un nouveau terme pour définir l'état végétatif : le « syndrome d'éveil non répondant »[22]. Ce nouveau terme a été proposé afin d'éviter la connotation négative intrinsèque du terme « végétatif ». Le patient en état végétatif/non répondant ne présente que des comportements dits réflexes, aucun comportement volontaire n'est donc observé. Cet état peut être transitoire, le patient évoluera alors vers un état de conscience minimale ou récupérera une conscience normale. La plupart des patients en état végétatif/non répondant récupèrent un certain degré de conscience dans le mois qui suit l'accident. Cependant, si le patient est toujours en état végétatif/non répondant trois mois après un accident non-traumatique ou un an après un accident traumatique, ses chances de récupération sont proches de zéro[23] et le patient est déclaré en état végétatif/non répondant *permanent*[24]. Des cas rares de récupération après ces délais ont néanmoins déjà été rapportés dans la littérature[25]. Certaines études ont mis en évidence que la présence de lésions dans le corps calleux et le tronc cérébral est un indicateur de mauvais pronostic chez des patients dont la cause de l'état végétatif/non répondant est traumatique[26].

L'EEG des patients en état végétatif/non répondant est caractérisé par un ralentissement généralisé de l'activité électrique cérébrale. Le tronc cérébral est relativement préservé (ce qui explique la préservation de l'éveil et des fonctions autonomes), tandis que les matières blanche et grise des deux hémisphères

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22 S. Laureys, G.G. Celesia, F. Cohadon, J. Lavrijsen, J. Leon-Carrion, W.G. Sannita, L. Sazbon, E. Schmutzhard, K.R. von Wild, A. Zeman et G. Dolce, « Unresponsive wakefulness syndrome : a new name for the vegetative state or apallic syndrome », *BMC Med*, 2010, 8, p. 68.

23 The Multi-Society Task Force on PVS, « Medical aspects of the persistent vegetative state (1) », *N Engl J Med*, 1994, 330(21), pp. 1499-1508.

24 S. Laureys, A.M. Owen et N.D. Schiff, « Brain function in coma, vegetative state, and related disorders », *Lancet Neurol*, 2004b, 3(9), pp. 537-546.

25 N. L. Childs et W.N. Mercer, « Late improvement in consciousness after post-traumatic vegetative state », *N Engl J Med*, 1996a, 334(1), pp. 24-25.

26 A. Kampfl, G. Franz, F. Aichner, B. Pfausler, H.P. Haring, S. Felber, G. Luz, M. Schocke et E. Schmutzhard, « The persistent vegetative state after closed head injury : clinical and magnetic resonance imaging findings in 42 patients », *J Neurosurg*, 1998, 88(5), pp. 809-816 ; A. Carpentier, D. Galanaud, L. Puybasset, J.C. Muller, T. Lescot, A.L. Boch, V. Riedl, P. Cornu, P. Coriat, D. Dormont et R. van Effenterre, « Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect « invisible brain stem damage » and predict « vegetative states », *J Neurotrauma*, 2006, 23(5), pp. 674-685.

sont sévèrement atteintes[27]. Des études réalisées en tomographie à émission de positons (TEP) ont démontré que les patients en état végétatif/non répondant souffraient d'une diminution importante du métabolisme cérébral global, allant jusqu'à 40 à 50 % en dessous de la normale[28]. Cependant, le métabolisme global seul ne peut expliquer l'absence de conscience chez les patients en état végétatif/non répondant, puisque certains patients qui récupèrent ne démontrent pas de changement au niveau de leur activité cérébrale globale mesurée en TEP et que certains sujets sains éveillés présentent une activité cérébrale globale similaire à celle des patients en état végétatif/non répondant[29]. En réalité, l'état végétatif/non répondant se caractérise par un dysfonctionnement, non pas de l'entièreté du cerveau, mais plutôt d'un réseau nommé *fronto-pariétal*, comprenant les cortex associatifs polymodaux, c'est-à-dire les régions frontales latérales bilatérales, les aires pariéto-temporales et pariétales postérieures, ainsi que les cortex mésio-frontal, postérieur cingulaire et précunéal[30]. Cependant, ces études ne permettent pas de définir l'activité neuronale spécifique à certains mécanismes cognitifs. C'est pourquoi l'activité cérébrale en réponse à des stimulations auditives, visuelles et tactiles a été étudiée chez les patients en état végétatif/non répondant. La perception de ce type de stimuli nécessite une capacité de conscience qui est, par définition, absente chez ces patients. L'absence de réactions comportementales ne peut toutefois pas être considérée comme une preuve absolue d'absence de conscience[31]. Plusieurs travaux réalisés en imagerie par résonance magnétique fonctionnelle (IRMf)[32] ont confirmé les résultats précédemment obtenus en TEP démontrant une activité cérébrale

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27 A. Owen, N.D. Schiff et S. Laureys, « The Assessment of Conscious Awareness in the Vegetative State », *in The Neurology of Counsciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 163-190.

28 S. Laureys, C. Lemaire, P. Maquet, C. Phillips et G. Franck, « Cerebral metabolism during vegetative state and after recovery to consciousness », *J Neurol Neurosurg Psychiatry*, 1999, 67(1), p. 121.

29 *Ibid.*

30 S. Laureys, M.E. Faymonville, X. De Tiege, P. Peigneux, J. Berre, G. Moonen, S. Goldman et P. Maque, « Brain function in the vegetative state », *Adv Exp Med Biol*, 2004a, 550, pp. 229-238.

31 J.L. Bernat, « The boundaries of the persistent vegetative state », *J Clin Ethics*, 1992, 3(3), pp. 176-180.

32 M.R. Coleman, J.M. Rodd, M.H. Davis, I.S. Johnsrude, D.K. Menon, J.D. Pickard et A.M. Owen, « Do vegetative patients retain aspects of language comprehension ? Evidence from fMRI », *Brain*, 2007, 130(10), pp. 2494-2507 ; H.B. Di, S.M. Yu, X.C. Weng, S. Laureys, D. Yu, J.Q. Li, P.M. Qin, Y.H. Zhu, S.Z. Zhang et Y.Z. Chen, « Cerebral response to patient's own name in the vegetative and minimally conscious states », *Neurology*, 2007, 68(12), pp. 895-899 ; D. Fernandez-Espejo, C. Junque, P. Vendrell, M. Bernabeu, T. Roig, N. Bargallo et J.M. Mercader, « Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury », *Brain Inj*, 2008, 22(11), pp. 882-890.

préservée des cortex sensoriels primaires, mais déconnectée de l'ensemble des aires associatives de haut niveau chez les patients en état végétatif/non répondant, et ce, aussi bien lors de stimulations auditives[33] que somatosensorielles[34]. Ces résultats suggèrent que la perception des stimuli environnants est altérée chez les patients en état végétatif/non répondant.

3.4. *État de conscience minimale*

Certains patients sévèrement cérébrolésés démontrent des signes limités mais clairs de conscience de leur environnement. L'état de conscience minimale se distingue de l'état végétatif/non répondant par la présence de comportements conscients reproductibles et soutenus (Tableau 1, p. 28). Malgré que le patient en état de conscience minimale soit incapable d'exprimer ses pensées et son ressenti, il démontre toutefois au moins un des comportements suivants : localisation de stimulations nociceptives, poursuite visuelle, comportements émotionnels adaptés au contexte, réponse à des commandes simples (par exemple : serrer la main, ouvrir la bouche, etc.) et/ou des verbalisations intelligibles[35]. Tout comme l'état végétatif/non répondant, l'état de conscience minimale peut être transitoire ou chronique. Cependant, il n'existe actuellement aucun critère permettant de parler d'*état de conscience minimale permanent*. Certains patients peuvent rester dans cet état durant plusieurs années et récupérer peu à peu une conscience normale comme observé par exemple chez le patient américain Terry Wallis[36]. L'émergence de l'état de conscience minimale est caractérisée par la présence fiable et consistante d'une communication fonc-

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33 S. Laureys, M.E. Faymonville, C. Degueldre, G.D. Fiore, P. Damas, B. Lambermont, N. Janssens, J. Aerts, G. Franck, A. Luxen, G. Moonen, M. Lamy et P. Maquet, « Auditory processing in the vegetative state », *Brain*, 2000, 123 (Pt 8), pp. 1589-1601 ; M. Boly, M.E. Faymonville, P. Peigneux, B. Lambermont, P. Damas, G. Del Fiore, C. Degueldre, G. Franck, A. Luxen, M. Lamy, G. Moonen, P. Maquet et S. Laureys, « Auditory processing in severely brain injured patients : differences between the minimally conscious state and the persistent vegetative state », *Arch Neurol*, 2004, 61(2), pp. 233-238.

34 M. Boly, M.E. Faymonville, C. Schnakers, P. Peigneux, B. Lambermont, C. Phillips, P. Lancellotti, A. Luxen, M. Lamy, G. Moonen, P. Maquet et S. Laureys, « Perception of pain in the minimally conscious state with PET activation : an observational study », *Lancet Neurol*, 2008a, 7(11), pp. 1013-1020.

35 J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J.H. Rosenberg, J. Whyte, R.D. Zafonte et N.D. Zasler, « The minimally conscious state : definition and diagnostic criteria », *Neurology*, 2002, 58(3), pp. 349-353.

36 H.U. Voss, A.M. Uluc, J.P. Dyke, R. Watts, E.J. Kobylarz, B.D. McCandliss, L.A. Heier, B.J. Beattie, K.A. Hamacher, S. Vallabhajosula, S.J. Goldsmith, D. Ballon, J.T. Giacino et N.D. Schiff, « Possible axonal regrowth in late recovery from the minimally conscious state », *J Clin Invest*, 2006, 116(7), pp. 2005-2011.

tionnelle ou d'une utilisation fonctionnelle de deux objets de la vie courante[37] (Figure 2). Les critères de l'état de conscience minimale étant encore assez récents, il existe peu d'études réalisées avec ces patients. Il semblerait toutefois que le pronostic de récupération des patients en état de conscience minimale soit plus favorable que celui des patients en état végétatif/non répondant[38]. Des études proposent que la réapparition d'une poursuite visuelle pourrait prédire la récupération progressive d'autres signes de conscience[39].

Figure 2

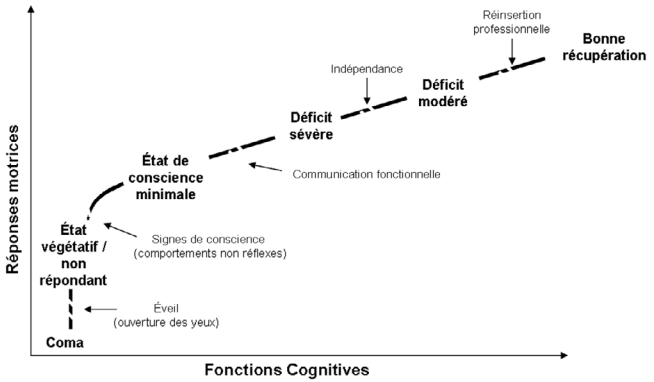


Schéma représentant l'évolution classique du coma vers une récupération fonctionnelle[40].

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37 J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J.H. Rosenberg, J. Whyte, R.D. Zafonte et N.D. Zasler, « The minimally conscious state : definition and diagnostic criteria », *Neurology*, 2002, 58(3), pp. 349-353.

38 J.T. Giacino et K. Kalmar, « The vegetative and minimally conscious states : A comparison of clinical features and functional outcome », *J Head Trauma Rehabil*, 1997, 12, pp. 36-51.

39 B.J. Ansell et J.E. Keenan, « The Western Neuro Sensory Stimulation Profile : a tool for assessing slow-to-recover head-injured patients », *Arch Phys Med Rehabil*, 1989, 70(2), pp. 104-108 ; J.T. Giacino et K. Kalmar, « The vegetative and minimally conscious states : A comparison of clinical features and functional outcome », *J Head Trauma Rehabil*, 1997, 12, pp. 36-51 ; A. Shiel, S.A. Horn, Wilson, B.A., Watson, M.J., Campbell, M.J. et McLellan, D.L., « The Wessex Head Injury Matrix (WHIM) main scale : a preliminary report on a scale to assess and monitor patient recovery after severe head injury », *Clin Rehabil*, 2000, 14(4), pp. 408-416 ; A. Shiel, S.A. Horn, Wilson, B.A., Watson, M.J., Campbell, M.J. et McLellan, D.L., « The Wessex Head Injury Matrix (WHIM) main scale : a preliminary report on a scale to assess and monitor patient recovery after severe head injury », *Clin Rehabil*, 2000, 14(4), pp. 408-416.

40 Adapté de A. Vanhaudenhuyse, « Vegetative state », *Scholarpedia*, 2009, 4, p. 4163.

L'EEG de patients en état de conscience minimale démontre un ralentissement général de l'activité électrique du cerveau. Les études réalisées en TEP démontrent que l'activité du précunéus ainsi que celle du cortex cingulaire postérieur permet de différencier l'état végétatif/non répondant de l'état de conscience minimale[41] (le métabolisme cérébral de ces régions est plus élevé chez les patients en état de conscience minimale que chez les patients en état végétatif/non répondant). De la même manière, une récente étude réalisée avec des patients traumatiques chroniques démontre que les régions fronto-basales médianes et préfrontales médianes, le précunéus et le thalamus sont davantage hypométaboliques chez les patients en état végétatif/non répondant que chez ceux en état de conscience minimale[42]. Par ailleurs, contrairement à l'état végétatif/non répondant, l'état de conscience minimale est caractérisé par une activité cérébrale corticale de haut niveau similaire à celle observée chez des sujets sains contrôles en réponse à des stimulations auditives[43] et nociceptives[44]. Des stimuli auditifs ayant une valence émotionnelle[45] (tels que des cris de bébé ou un récit narré par la mère du patient) induisent une activité cérébrale significativement plus étendue chez les patients en état de conscience minimale que des stimuli neutres. L'ensemble de ces données suggère d'une part, que le traitement analgésique des patients en état de conscience minimale ne doit pas être négligé, et d'autre part, que le contenu de nos paroles est important lorsque nous parlons à proximité ou directement au patient.

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41 S. Laureys, A.M. Owen et N.D. Schiff, « Brain function in coma, vegetative state, and related disorders », *Lancet Neurol*, 2004b, 3(9), pp. 537-546.

42 N. Nakayama, A. Okumura, J. Shinoda, T. Nakashima et T. Iwama, « Relationship between regional cerebral metabolism and consciousness disturbance in traumatic diffuse brain injury without large focal lesions: an FDG-PET study with statistical parametric mapping analysis », *J Neurol Neurosurg Psychiatry*, 2006, 77(7), pp. 856-862.

43 M. Boly, M.E. Faymonville, P. Peigneux, B. Lambermont, F. Damas, A. Luxen, M. Lamy, G. Moonen, P. Maquet et S. Laureys, « Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS », *Neuropsychol Rehabil*, 2005, 15(3-4), pp. 283-289.

44 M. Boly, M.E. Faymonville, C. Schnakers, P. Peigneux, B. Lambermont, C. Phillips, P. Lancellotti, A. Luxen, M. Lamy, G. Moonen, P. Maquet et S. Laureys, « Perception of pain in the minimally conscious state with PET activation: an observational study », *Lancet Neurol*, 2008a, 7(11), pp. 1013-1020.

45 S. Laureys, F. Perrin, M.E. Faymonville, C. Schnakers, M. Boly, V. Bartsch, S. Majerus, G. Moonen et P. Maquet, « Cerebral processing in the minimally conscious state », *Neurology*, 2004c, 63(5), pp. 916-918; N.D. Schiff, D. Rodriguez-Moreno, A. Kamal, K.H. Kim, J.T. Giacino, F. Plum et J. Hirsch, « fMRI reveals large-scale network activation in minimally conscious patients », *Neurology*, 2005, 64(3), pp. 514-523.

3.5. *Locked-in* syndrome

Le *locked-in* syndrome, ou syndrome de verrouillage, doit être considéré comme une pathologie à part entière des états de conscience altérée. Le tableau clinique des patients en *locked-in* syndrome est défini comme suit : « un patient conscient, associant : la présence d'une ouverture continue des paupières (en l'absence de ptôsis bilatéral, auquel cas l'examinateur devra ouvrir manuellement les yeux du patient), des capacités cognitives relativement intactes[46], une aphonie ou une hypophonie sévère, une quadriplégie ou une quadriparésie, et une communication basée principalement sur les mouvements oculo-palpébraux »[47] (Tableau 1, p. 28). Cette pathologie peut être divisée en trois catégories selon l'étendue du handicap moteur et verbal[48] : le *locked-in syndrome classique* qui est caractérisé par une immobilité totale à l'exception du mouvement vertical des yeux et du clignement des paupières ; le *locked-in syndrome incomplet* qui bénéficie de quelques reliquats de motricité volontaire et le *locked-in syndrome complet* qui implique une immobilité complète, s'étendant à l'ensemble de la motricité oculaire. Le taux de mortalité chez des patients atteints de *locked-in* syndrome en stade aigu s'élève à 76 % pour les causes vasculaires et 41 % pour les causes non-vasculaires ; 87 % des patients décédent dans les quatre premiers mois après l'accident[49]. Les informations issues de la base de données de l'Association du *Locked-In* Syndrome (ALIS) indiquent que les patients qui survivent à l'atteinte cérébrale sont plus jeunes que les patients qui décèdent[50]. La durée de vie moyenne est de

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46 C. Schnakers, S. Majerus, S. Goldman, M. Boly, P. Van Eeckhout, S. Gay, F. Pellas, V. Bartsch, P. Peigneux, G. Moonen et S. Laureys, « Cognitive function in the *locked-in* syndrome », *J Neurol*, 2008b, 255(3), pp. 323-330.

47 American Congress of Rehabilitation Medicine, « Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness », *Arch Phys Med Rehabil*, 1995, 76, pp. 205-209.

48 G. Bauer, F. Gerstenbrand et E. Rumpl, « Varieties of the *locked-in* syndrome », *J Neurol*, 1979, 221(2), pp. 77-91.

49 J.R. Patterson et M. Grabois, « Locked-in syndrome : a review of 139 cases », *Stroke*, 1986, 17(4), pp. 758-764.

50 O. Gosseries, M.A. Bruno, A. Vanhaudenhuyse, S. Laureys et C. Schnakers, « Consciousness in the Locked-in Syndrome », *in The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi. Oxford, Elsevier, 2009, pp. 191-203.

6±4 ans[51]. Même s'il existe de rares cas de récupération complète[52], la majorité des patients souffrent de déficits moteurs sévères. Afin d'améliorer leur capacité à interagir avec leur entourage et subséquemment leur qualité de vie, divers systèmes d'interfaces cerveau/ordinateur ont été validés et d'autres sont toujours en cours de création[53].

Les causes les plus fréquentes du *locked-in* syndrome sont l'occlusion de l'artère basilaire et l'hémorragie pontine. Cependant, d'autres étiologies ne doivent pas être exclues, telles qu'un traumatisme crânien suivi de lésions du tronc cérébral ou d'une artère vertébrale, une occlusion d'une artère vertébrobasilaire ou encore une compression des pédoncules cérébraux par hernie tentorielle[54]. Le *locked-in* syndrome complet est également observé en fin de sclérose latérale amyotrophique. D'autres cas de *locked-in* syndrome, plus rares, sont parfois causés par une hémorragie subarachnoïdale avec des spasmes de l'artère basilaire, une tumeur du tronc cérébral, une myélinolyse centropontine, une encéphalite, un abcès de la protubérance, une intoxication au niveau du tronc cérébral, une réaction à un vaccin ou encore une hypoglycémie prolongée. Des cas de *locked-in* syndromes complets temporaires ont également été signalés après un syndrome de Guillain- Barré ou des polyneurophaties post-infectieuses sévères. Des cas de *locked-in* réversibles peuvent aussi être observés lorsque le patient reçoit du curare avec une dose insuffisante d'anesthésiants[55]. Les résultats d'enregistrements EEG chez des patients atteints du *locked-in* syndrome sont très hétérogènes. En effet, certaines études ont montré que les tracés EEG de ces patients étaient normaux ou légèrement plus lents, avec une activité alpha réactive et normalement

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51 Intervalle entre 14 jours et 29 ans – O. Gosseries, M.A. Bruno, A. Vanhaudenhuyse, S. Laureys et C. Schnakers, « Consciousness in the Locked-in Syndrome », *in The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi. Oxford, Elsevier, 2009, pp. 191-203.

52 L. Bohn-Derrien, *Je parle. L'extraordinaire retour à la vie d'un locked-in syndrom*, Paris, 2005.

53 A. Kübler, « Brain-Computer Interfaces for Communication in Paralysed Patients and Implications for Disorders of Consciousness », *in The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 217-233.

54 S. Laureys, F. Pellas, P. Van Eeckhout, S. Ghorbel, C. Schnakers, F. Perrin, J. Berre, M.E. Faymonville, K.H. Pantke, F. Damas, M. Lamy, G. Moonen et S. Goldman, « The *locked-in* syndrome : what is it like to be conscious but paralyzed and voiceless ? », *Prog Brain Res*, 2005, 150, pp. 495-511.

55 M.A. Bruno, F. Pellas, J.L. Bernheim, D. Ledoux, S. Goldman, A. Demertzi, S. Majerus, A. Vanhaudenhuyse, V. Blandin, M. Boly, P. Boveroux, G. Moonen, S. Laureys et C. Schnakers, « Life with Locked-In syndrome », *Rev Med Liege*, 2008, 63(5-6), pp. 445-451.

distribuée[56] ; alors que d'autres études notent un ralentissement diffus du signal EEG chez la moitié des patients[57] ; ou encore un rythme alpha non réactif aux stimuli multimodaux[58]. Cette hétérogénéité des résultats souligne que l'absence d'un rythme alpha réactif ne peut être considérée comme un indicateur sûr d'absence de conscience. Dès lors, nous ne pouvons pas nous fier à cet indice EEG pour différencier un patient en *locked-in* syndrome d'un patient en coma suite à une lésion du tronc cérébral. Cependant, face à la présence d'un rythme alpha préservé chez un patient manifestement inconscient, nous ne pouvons pas écarter l'hypothèse que ce patient soit en *locked-in* syndrome.

Les données obtenues en neuroimagerie indiquent une absence de diminution significative du métabolisme cérébral chez les patients *locked-in* par rapport à celle des sujets contrôles[59]. L'imagerie cérébrale structurelle peut révéler des lésions isolées de la portion ventrale de la base du pont ou du mésencéphale chez les patients atteints d'un *locked-in* syndrome[60]. Une hyperactivité significative de l'amygdale est également observée en stade aigu. Nous savons, par des travaux réalisés sur les émotions négatives, que la peur et l'anxiété provoquent une activation significative de l'amygdale[61]. Dès lors, nous pouvons supposer que l'augmentation de l'activité de la région amygdalienne observée chez les patients en *locked-in* syndrome en phase initiale est liée à cette situation particulière, à savoir être conscient mais prisonnier d'un corps inerte et incapable de communiquer aisément. Il est donc nécessaire de diagnostiquer correctement et le plus rapidement possible le *locked-in*

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56 O.N. Markand, « Electroencephalogram in « *locked-in* » syndrome », *Electroencephalogr Clin Neurophysiol*, 1976, 40(5), pp. 529-534 ; C. Bassetti, J. Mathis et C.W. Hess, « Multimodal electrophysiological studies including motor evoked potentials in patients with locked-in syndrome : report of six patients », *J Neurol Neurosurg Psychiatry*, 1994, 57(11), pp. 1403-1406.

57 J.R. Patterson et M. Grabois, « Locked-in syndrome : a review of 139 cases », *Stroke*, 1986, 17(4), pp. 758-764.

58 D.E. Jacome et D. Morilla-Pastor, « Unreactive EEG : pattern in locked-in syndrome », *Clin Electroencephalogr*, 1990, 21(1), pp. 31-36 ; E. Gutling, S. Isenmann et W. Wichmann, « Electrophysiology in the locked-in-syndrome », *Neurology*, 1996, 46(4), pp. 1092-1101.

59 S. Laureys, A.M. Owen et N.D. Schiff, « Brain function in coma, vegetative state, and related disorders », *Lancet Neurol*, 2004b, 3(9), pp. 537-546.

60 J. Leon-Carrion, P. van Eeckhout, M. Dominguez-Morales, R. Del et F.J. Perez-Santamaria, « The locked-in syndrome : a syndrome looking for a therapy », *Brain Inj*, 2002, 16(7), pp. 571-582.

61 A.J. Calder, A.D. Lawrence et A.W. Young, « Neuropsychology of fear and loathing », *Nat Rev Neurosci*, 2001, 2(5), pp. 352-363.

syndrome afin d'adapter la prise en charge thérapeutique aussi bien médicamenteuse que comportementale.

Tableau I

Critères diagnostiques des états de conscience altérée et du *locked-in* syndrome[62]

Mort cérébrale
• Coma profond non réactif à des stimuli nociceptifs • Absence de facteurs confondants (troubles hypothermique, médicamenteux, électrolyte, endocrinien) • Absence des réflexes du tronc cérébral • Absence de réponse motrice • Apnée • Réévaluation dans les 6 heures • Examens complémentaires confirmatifs
Coma
• Aucune ouverture des yeux même lors de stimulations nociceptives • Aucune démonstration de conscience de soi ou de l'environnement • Durée d'au moins une heure
État végétatif /non répondant
• Aucun signe de conscience de soi et de l'environnement • Incapacité à interagir avec l'environnement • Aucun comportement soutenu, reproductible et volontaire en réponse à des stimuli visuel, auditif, tactile ou nociceptif • Aucune compréhension ou expression langagière • Présence d'un cycle veille-sommeil • Préservation des fonctions autonomes hypothalamiques et du tronc cérébral permettant de vivre uniquement avec des soins infirmiers et médicaux • Incontinence urinaire et fécale • Préservation variable des réflexes spinaux et crâniens

62 Adapté de A. Vanhaudenhuyse, « Vegetative state », *Scholarpedia*, 2009, 4, p. 4163.

État de conscience minimale
Évidence claire d'une conscience sur base de la présence soutenue et reproductible d'au moins un des comportements suivants : • Comportements adaptés au contexte (incluant les comportements à connotation affective apparaissant en réponse à des stimuli environnementaux) tels que : – poursuite visuelle ou fixation soutenue d'un stimulus – sourire ou pleur en réponse à des stimuli verbaux ou visuels émotionnels – localisation nociceptive – atteinte d'un objet placé dans le champ visuel – préhension d'un objet adaptée à ses forme et taille – vocalisations ou gestes en réponse à une question – réponse à des commandes simples – réponses oui/non verbales ou non-verbales (indépendantes de leur justesse) – verbalisations intelligibles
Émergence de l'état de conscience minimale
Récupération d'un des comportements suivants : • Communication fonctionnelle • Capacité à utiliser fonctionnellement des objets
Locked-in *syndrome*
• Ouverture des yeux soutenue (un ptôsis bilatéral doit être exclu si aucune ouverture des yeux n'est observée) • Aphonie ou hypophonie • Quadriplégie ou quadriparésie • Communication via des mouvements oculaires verticaux ou latéraux, ou par clignements des paupières • Conscience préservée

4. L'évaluation clinique de la conscience

Même si diverses technologies sont de plus en plus utilisées, l'évaluation clinique comportementale reste la méthode principale pour détecter la conscience au chevet du patient[63]. L'évaluation de la conscience des patients

63 S. Majerus, H. Gill-Thwaites, K. Andrews et S. Laureys, « Behavioral evaluation of consciousness in severe brain damage », *Prog Brain Res*, 2005, 150, pp. 397-413.

sévèrement cérébro-lésés lors de leur admission et tout au long de leur hospitalisation est essentielle pour obtenir des informations sur leur progression et pour définir une future prise en charge appropriée. Différencier un comportement volontaire d'un comportement réflexe chez des patients incapables de communiquer demeure cependant un véritable défi. Il y a une dizaine d'années, 37 à 43 % des patients étaient erronément diagnostiqués comme étant en état végétatif/non répondant alors qu'ils présentaient en réalité des signes de conscience[64]. Dans une étude récente, nous avons démontré que le taux de diagnostic erroné d'état végétatif/non répondant s'élevait toujours à 41 %, et ce malgré l'introduction de nouveaux critères de l'état de conscience minimale en 2002[65]. Les diagnostics de coma ou d'état végétatif/non répondant peuvent également être attribués à tort à des patients atteints d'un *locked-in* syndrome[66]. Plusieurs récits témoignent de cette situation, comme le décrit Julia Tavalaro[67], patiente *locked-in* considérée par le personnel soignant comme étant un *légume* pendant plus de six ans. Dans ces cas, la difficulté à établir un diagnostic peut être due à la rareté de ce syndrome, à la difficulté de reconnaître des signes de conscience[68], à une fluctuation de la vigilance typiquement observée chez ces patients en stade aigu ou encore à des déficits cognitifs[69] ou sensoriels additionnels tels qu'une aphasie ou une surdité[70]. Un mauvais diagnostic peut avoir des conséquences désastreuses quant à la prise en charge de ces patients. Plusieurs échelles comportementales standar-

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64 K. Andrews, L. Murphy, R. Munday et C. Littlewood, « Misdiagnosis of the vegetative state : retrospective study in a rehabilitation unit », *BMJ*, 1996, 313(7048), pp. 13-16 ; N. L. Childs et W.N. Mercer, « Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs [letter ; comment] », *BMJ*, 1996b, 313(7062), p. 944.

65 C. Schnakers, A. Vanhaudenhuyse, J.T. Giacino, M. Ventura, M. Boly, S. Majerus, G. Moonen et S. Laureys, « Diagnostic accuracy of the vegetative and minimally conscious state : clinical consensus versus standardized neurobehavioral assessment », *BMC Neurol*, 2009b, 9, p. 35.

66 M.A. Bruno, C. Schnakers, F. Damas, F. Pellas, I. Lutte, J. Bernheim, S. Majerus, G. Moonen, S. Goldman et S. Laureys, « Locked-in syndrome in children : report of five cases and review of the literature », *Pediatr Neurol*, 2009, 41(4), pp. 237-246.

67 J. Tavalaro. et R. Tayson, *Look up for yes*, New York, NY, Kodansha America, Inc., 1997.

68 S. Majerus, H. Gill-Thwaites, K. Andrews et S. Laureys, « Behavioral evaluation of consciousness in severe brain damage », *Prog Brain Res*, 2005, 150, pp. 397-413.

69 C. Schnakers, S. Majerus, S. Goldman, M. Boly, P. Van Eeckhout, S. Gay, F. Pellas, V. Bartsch, P. Peigneux, G. Moonen et S. Laureys, « Cognitive function in the locked-in syndrome », *J Neurol*, 2008b, 255(3), pp. 323-330.

70 M.A. Bruno, C. Schnakers, F. Damas, F. Pellas, I. Lutte, J. Bernheim, S. Majerus, G. Moonen, S. Goldman et S. Laureys, « Locked-in syndrome in children : report of five cases and review of the literature », *Pediatr Neurol*, 2009, 41(4), pp. 237-246.

disées sont utilisées dans l'évaluation de la conscience des patients sévèrement cérébrolésés.

4.1. *La* Glasgow Coma Scale *(GCS)*

La *Glasgow Coma Scale*[71] est l'échelle de référence reconnue internationalement. Elle évalue rapidement à la fois les comportements spontanés et les comportements induits par une stimulation. Elle est utilisée dès l'entrée des patients à l'hôpital et tout au long de leur hospitalisation aux soins intensifs. La GCS est principalement intéressante pour suivre l'évolution des patients dans les stades aigus. Elle se compose de trois parties : l'ouverture des yeux (« E ») qui mesure l'éveil, la réponse verbale («V ») qui mesure le degré d'intégrité du système nerveux et la réponse motrice (« M ») qui mesure l'intégrité du système moteur[72]. L'addition des valeurs de ces trois critères donne un score total compris entre 3 et 15. En stade aigu, l'atteinte cérébrale est qualifiée de « grave » si le score est inférieur ou égal à 8, « modérée » si le score se situe entre 9 et 12 et « légère » si le score est supérieur ou égal à 13[73]. Les patients sont souvent diagnostiqués en coma si leur score est égal ou inférieur à 8[74]. Pour prédire l'évolution à court terme du patient, le score à l'échelle motrice serait le meilleur prédicteur[75], mais cette sous-échelle serait également la plus difficile à évaluer. Malgré son succès international, les cliniciens ont rapidement été confrontés aux limites de cette échelle[76]. Par exemple, la composante verbale ne peut être évaluée chez les patients intubés. L'information fournie s'en trouve dès lors tronquée. De plus, la GCS n'envisage

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71 G. Teasdale et B. Jennett, « Assessment of coma and impaired consciousness. A practical scale », *Lancet*, 1974, 2(7872), pp. 81-84.

72 K. Prasad, « The Glasgow Coma Scale : a critical appraisal of its clinimetric properties », *J Clin Epidemiol*, 1996, 49(7), pp. 755-763.

73 Recommandations pour la pratique clinique, « Prise en charge des traumatisés crâniens graves à la phase précoce », *Ann Fr Anesth Réanim*, 1999, 18, pp. 27-35.

74 M. Watson, S. Horn et J. Curl, « Searching for signs of revival. Uses and abuses of the Glasgow coma scale », *Prof Nurse*, 1992, 7(10), pp. 670-674.

75 J. Jagger, J.A. Jane et R. Rimel, « The Glasgow coma scale : to sum or not to sum ? », *Lancet*, 1983, 2(8341), p. 97.

76 J. Jagger, J.A. Jane et R. Rimel, « The Glasgow coma scale : to sum or not to sum ? », *Lancet*, 1983, 2(8341), p. 97 ; G. Rowley et K. Fielding, « Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users », *Lancet*, 1991, 337(8740), pp. 535-538 ; D. Moskopp, C. Stahle et H. Wassmann, « Problems of the Glasgow Coma Scale with early intubated patients », *Neurosurg Rev*, 1995, 18(4), pp. 253-257.

pas l'évaluation des réflexes du tronc cérébral, ce qui entraîne une perte d'information non négligeable dans le diagnostic et le pronostic des patients cérébrolésés.

4.2. *La* Glasgow Liège Scale *(GLS)*

La *Glasgow Liège Scale*[77] est identique à la GCS mais elle évalue en plus les réflexes du tronc cérébral (« R » sur 5 points). Ces réflexes comprennent les réflexes fronto-orbiculaires, oculovestibulaires verticaux et horizontaux, pupillaires et oculocardiaques. La GLS évalue plus précisément l'altération encéphalique que la GCS. L'évaluation des réflexes permet en effet de mesurer la désintégration progressive des fonctions du tronc cérébral. Ils disparaissent pendant la détérioration rostro-caudale de façon hiérarchique[78]. Dans les premières 24 heures après la lésion, l'étude des réflexes du tronc cérébral semble être le meilleur prédicteur de l'évolution. Pour les lésions traumatiques, les réflexes du tronc cérébral sont presque toujours revenus à la normale dans les deux semaines qui suivent le traumatisme, peu importe que l'évolution finale soit positive ou négative. La GLS a une sensibilité comparable à celle de la GCS pour évaluer le passage du coma à l'éveil[79] mais sa prédictibilité semble meilleure[80]. Les deux critiques adressées à la GCS, concernant un score maximal différent pour chaque sous-échelle et une administration non systématique de toutes les sous-échelles, sont également valables pour la GLS.

4.3. *La* Full Outline of Unresponsiveness *(FOUR)*

Récemment, l'échelle *Full Outline of UnResponsiveness – FOUR*[81] a été validée et proposée pour remplacer la GCS. La FOUR se divise en 4 sous-échelles : motrice (« M »), visuelle (« E »), réflexes du tronc cérébral (« B ») et respiration (« R »). Les réflexes du tronc cérébral sont les réflexes pupillaires,

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77 J.D. Born, P. Hans, G. Dexters, K. Kalangu, J. Lenelle, G. Milbouw et A. Stevenaert, « Practical assessment of brain dysfunction in severe head trauma », *Neurochirurgie*, 1982, 28(1), pp. 1-7.

78 *Ibid.*

79 J.D. Born, A. Albert, P. Hans et J. Bonnal, « Relative prognostic value of best motor response and brain stem reflexes in patients with severe head injury », *Neurosurgery*, 1985, 16(5), pp. 595-601.

80 J.D. Born, « The Glasgow-Liège Scale. Prognostic value and evaluation of motor response and brain stem reflexes after severe head injury », *Acta Neurochir*, 1988, 95, pp. 49-52.

81 E.F. Wijdicks, W.R. Bamlet, B.V. Maramattom, E.M. Manno et R.L. McClelland, « Validation of a new coma scale : The FOUR score », *Ann Neurol*, 2005, 58(4), pp. 585-593.

cornéens et de toux. L'intérêt de la FOUR est que sa passation est courte et qu'elle peut être facilement utilisée dans les unités de soins intensifs[82]. La FOUR a été spécifiquement développée pour détecter l'état végétatif/non répondant, le *locked-in* syndrome et la mort cérébrale et, contrairement à la GCS, elle n'inclut pas l'évaluation des fonctions verbales[83]. Par ailleurs, la FOUR évalue la poursuite visuelle, premier signe de conscience réapparaissant chez les patients en état de conscience minimale[84].

4.4. *La* Coma Recovery Scale-Revised *(CRS-R)*

La *Coma Recovery Scale-Revised – CRS-R*, proposée par Giacino et *al.*[85] est actuellement l'échelle la plus adaptée pour différencier les patients en état végétatif/non répondant des patients en état de conscience minimale. La CRS-R a été créée sur base des critères de l'état de conscience minimale et est plus performante que la GCS dans la détection des signes de conscience chez des patients non-communicants[86]. Cette échelle catégorielle est répartie en six sous-échelles (auditive, visuelle, motrice, oromotrice/verbale, communication et éveil). Le score se base sur la présence de comportements en réponse à des stimulations sensorielles. Le score total peut être calculé en additionnant la meilleure réponse observée dans chaque sous-échelle, mais il est préférable, comme pour la GCS et la GLS, de se baser sur le score de chaque sous-échelle. En effet, le diagnostic s'établit ici d'après la nature des comportements observés et non d'après le score total obtenu. Par exemple, si l'item « poursuite visuelle » est présent chez un patient, il sera considéré comme en état de conscience minimale. Les réflexes du tronc cérébral sont également mesurés. L'évaluation dure entre 10 et 60 minutes, dépendamment

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82 C. Schnakers, J. Giacino, K. Kalmar, S. Piret, E. Lopez, M. Boly, R. Malone et S. Laureys, « Does the FOUR score correctly diagnose the vegetative and minimally conscious states ? », *Ann Neurol*, 2006, 60(6), pp. 744-745.

83 E.F. Wijdicks, W.R. Bamlet, B.V. Maramattom, E.M. Manno et R.L. McClelland, « Validation of a new coma scale : The FOUR score », *Ann Neurol*, 2005, 58(4), pp. 585-593.

84 J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J.H. Rosenberg, J. Whyte, R.D. Zafonte et N.D. Zasler, « The minimally conscious state : definition and diagnostic criteria », *Neurology*, 2002, 58(3), pp. 349-353.

85 J.T. Giacino, K. Kalmar et J. Whyte, « The JFK Coma Recovery Scale-Revised : measurement characteristics and diagnostic utility », *Arch Phys Med Rehabil*, 2004, 85(12), pp. 2020-2029.

86 C. Schnakers, J. Giacino, K. Kalmar, S. Piret, E. Lopez, M. Boly, R. Malone et S. Laureys, « Does the FOUR score correctly diagnose the vegetative and minimally conscious states ? », *Ann Neurol*, 2006, 60(6), pp. 744-745.

de la réactivité du patient. Une version validée en français est désormais disponible[87].

4.5. *La* Wessex Head Injury Matrix *(WHIM)*

La *Wessex Head Injury Matrix – WHIM*[88] est une échelle ordinale qui se compose de 62 items ordonnés selon une séquence de récupération qui a été déterminée à partir de l'ordre de réapparition de différents signes et comportements chez 88 patients traumatisés sévères. Elle évalue les réponses réflexes et les réponses conscientes allant de peu élaborées à très élaborées (par exemple : l'item 1 est « ouverture brève des yeux » alors que l'item 58 est « utilise l'écriture, un clavier ou une autre aide de communication de manière fluente »). Cette échelle est surtout intéressante pour suivre l'évolution des patients depuis la sortie du coma jusqu'à la récupération de leur conscience et de leurs fonctions cognitives. Elle est également utile chez les patients en état de conscience minimale qui ne semblent plus évoluer selon les autres échelles comportementales. Elle permet également de fournir des informations utiles pour fixer des buts rééducatifs. L'objectif de la WHIM est de créer une transition entre l'évaluation du coma dans les stades aigus par la GCS/GLS et la réalisation de tests neuropsychologiques qui sont appliqués beaucoup plus tardivement[89]. L'évaluation se base sur l'observation de la présence ou non de certains comportements et elle dure entre 5 minutes et 1 heure. La WHIM couvre un large éventail de fonctions de la vie quotidienne en évaluant principalement les capacités motrices, les aptitudes cognitives (connaissance autobiographique, reconnaissance, compréhension, concentration et attention) et les interactions sociales, mais également l'état d'éveil et les modalités auditivo-verbale, visuelle et tactilo-motrice.

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87 C. Schnakers, S. Majerus, J. Giacino, A. Vanhaudenhuyse, M.A. Bruno, M. Boly, G. Moonen, P. Damas, B. Lambermont, M. Lamy, F. Damas, M. Ventura et S. Laureys, « A French validation study of the Coma Recovery Scale-Revised (CRS-R) », *Brain Inj*, 2008a, 22(10), pp. 786-792 – www.comascience.org.

88 S. Majerus et M. Van der Linden, « Wessex Head Injury Matrix and Glasgow/Glasgow-Liège Coma Scale : A validation and comparison study », *Neuropsychological Rehabilitation*, 2000, 10(2), pp. 167-184 ; A. Shiel, S.A. Horn, Wilson, B.A., Watson, M.J., Campbell, M.J. et McLellan, D.L., « The Wessex Head Injury Matrix (WHIM) main scale : a preliminary report on a scale to assess and monitor patient recovery after severe head injury », *Clin Rehabil*, 2000, 14(4), pp. 408-416.

89 *Ibid.*

4.6. Sensory Modality Assessment and Rehabilitation Technique *(SMART)*

La *Sensory Modality Assessment and Rehabilitation Technique – SMART*[90] a été créée par l'équipe de thérapie occupationnelle du *Royal Hospital for Neurodisability* à Londres comme outil diagnostique et d'évaluation de la récupération des patients en état de conscience altérée. La SMART semble utile pour le suivi des patients à long terme, car elle permet d'évaluer les réponses du patient à un nombre élevé de stimulations sensorielles, et ceci, dans différentes modalités, toutes cotées indépendamment les unes des autres[91]. Ces mêmes stimulations peuvent aussi être utilisées par la suite dans une phase de traitement. Un atout de cette échelle se situe dans l'intégration des observations et informations provenant de la famille, des proches et de l'équipe soignante, que ce soit concernant les habitudes du patient précédant l'accident ou les comportements observés au cours de l'hospitalisation. Ces informations sont importantes pour l'évaluation, et peuvent influer sur le choix des stimulations administrées au patient lors de la phase de traitement. Cependant, son utilisation clinique reste difficile, non seulement par le temps d'administration de l'échelle qui s'élève à au moins 45 minutes, mais aussi car le nombre d'évaluations (n=10) et le temps nécessaire à l'obtention d'un diagnostic est long. Elle n'est donc pas adaptée au contexte d'évaluation dans les unités de soins intensifs. De plus, les critères diagnostiques définis selon les 5 niveaux sont vastes ce qui ne permet pas d'établir un diagnostic précis et aucune étude n'a été réalisée actuellement pour comparer la SMART à la CRS-R, échelle qui a pourtant montré sa sensibilité par rapport à d'autres échelles.

4.7. *Évaluation de la conscience : outils spécifiques et comportements ambigus*

Comme nous l'avons précédemment expliqué, l'utilisation d'échelles comportementales permet aux cliniciens de statuer sur l'état de conscience des patients non communicants. Cependant, l'utilisation de différents stimuli pour tester des aptitudes identiques chez les patients est un des problèmes

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90 H. Gill-Thwaites et R. Munday, « The sensory modality assessment and rehabilitation technique (SMART) : a valid and reliable assessment for vegetative state and minimally conscious state patients », *Brain Inj*, 2004, 18(12), pp. 1255-1269.

91 C. Chatelle, C. Schnakers, M.A. Bruno, O. Gosseries, S. Laureys et A. Vanhaudenhuyse, « The Sensory Modality Assessment and Rehabilitation Technique (SMART) : a behavioral assessment scale for disorders of consciousness », *Rev Neurol (Paris)*, 2010, 166(8-9), pp. 675-682.

classiques rencontrés dans la pratique clinique. La poursuite visuelle, un des premiers signes de conscience réapparaissant chez les patients en état de conscience altérée[92], peut être évaluée de différentes manières selon l'échelle clinique employée (objet, personnes, miroir, etc.). Elle n'est parfois tout simplement pas testée comme c'est le cas dans la GCS et la GLS. Nous avons récemment démontré que la poursuite visuelle était significativement mieux détectée lorsqu'elle était évaluée à l'aide d'un miroir[93].

Par ailleurs, certains comportements sont encore difficiles à interpréter en termes de conscience. Tout comme l'utilisation d'outils non appropriés pour évaluer la conscience, l'absence de consensus à propos de la signification de certains comportements en termes de conscience peut mener à de mauvaises interprétations des réponses du patient. Le clignement à la menace visuelle est une méthode classiquement employée pour tester les processus visuels au chevet du patient. En réponse à un mouvement soudain en direction des yeux, une personne réagira normalement en fermant les yeux de manière momentanée. Pour certains auteurs, le clignement à la menace visuelle est un comportement traduisant une conscience, alors que d'autres postulent qu'une réponse à une menace visuelle est habituellement absente chez les patients en état végétatif/non répondant. Nous avons démontré que le réflexe de clignement à la menace visuelle était compatible avec le diagnostic d'état végétatif/non répondant et qu'il n'était pas un signe précurseur de bonne ou mauvaise récupération[94]. La fixation visuelle est également un comportement dont la signification peut être difficilement interprétable. Selon les critères de la CRS-R, une fixation visuelle est observée si les yeux du patient quittent le point de fixation de départ pour regarder un objet pendant plus de 2 secondes[95]. Grâce à l'étude du métabolisme cérébral par TEP, nous avons pu mettre en évidence que la présence d'une fixation visuelle, chez des patients anoxiques ne démontrant aucun autre compor-

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92 J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J.H. Rosenberg, J. Whyte, R.D. Zafonte et N.D. Zasler, « The minimally conscious state : definition and diagnostic criteria », *Neurology*, 2002, 58(3), pp. 349-353.

93 A. Vanhaudenhuyse, C. Schnakers, S. Bredart et S. Laureys, « Assessment of visual pursuit in post-comatose states : use a mirror », *J Neurol Neurosurg Psychiatry*, 2008b, 79(2), p. 223.

94 A. Vanhaudenhuyse, J.T. Giacino, C. Schnakers, K. Kalmar, C. Smart, M.A. Bruno, M.A., O. Gosseries, G. Moonen et S. Laureys, « Blink to visual threat does not herald consciousness in the vegetative state », *Neurology*, 2008a.

95 J.T. Giacino, « The vegetative and minimally conscious states : consensus-based criteria for establishing diagnosis and prognosis », *NeuroRehabilitation*, 2004, 19(4), pp. 293-298.

tement dit conscient, n'était pas accompagnée par une différence d'activité cérébrale ni par une différence de connectivité cortico-corticale par rapport à des patients en état végétatif/non répondant « typiques »[96] (c'est-à-dire ne démontrant pas de fixation visuelle). En effet, les patients ne présentant aucune fixation visuelle montraient un hypométabolisme des cortex associatifs fronto-temporo-pariétal et des thalami, tout comme les patients avec une fixation visuelle. Aucune différence de récupération de conscience n'a pu être décelée entre ces deux groupes de patients dont l'étiologie était anoxique. Ces résultats remettent donc en question l'inclusion de la fixation visuelle comme critère de conscience tel qu'admis dans certaines échelles d'évaluation comportementale.

5. Outils para-cliniques d'évaluation de la conscience

5.1. *Activité cérébrale spontanée*

Parallèlement à l'étude du métabolisme cérébral mesuré en TEP, une attention croissante est également portée à l'activité cérébrale spontanée, aussi appelée *réseau du mode par défaut*, ainsi qu'à sa signification comportementale et cognitive[97]. Ce réseau comprend des régions telles que le cortex cingulaire postérieur, le précunéus, les jonctions temporo-pariétales et le cortex préfrontal. L'ensemble de ces régions est caractérisé par une désactivation lors de tâches cognitives et une activation lorsque les sujets sont éveillés mais au repos, c'est-à-dire ne réalisant aucune tâche spécifiquement. Même si la fonction exacte du réseau du mode par défaut reste toujours au cœur de nombreux débats, certains travaux proposent que celui-ci joue un rôle de base dans le réseau neuronal de la conscience. L'intérêt clinique de l'étude du réseau du mode par défaut chez des patients en état de conscience altérée a été récemment démontré. Des premiers travaux ont mis en évidence qu'aucun réseau du mode par défaut n'a été détecté chez un patient en mort cérébrale[98] alors qu'une préservation partielle de la connectivité du réseau

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96 M.A. Bruno, A. Vanhaudenhuyse, C. Schnakers, M. Boly, O. Gosseries, A. Demertzi, S. Majerus, G. Moonen, R. Hustinx et S. Laureys, « Visual fixation in the vegetative state : an observational case series PET study », *BMC Neurol*, 2010b, 10(1), p. 35.

97 M.E. Raichle, « Neuroscience. The brain's dark energy », *Science*, 2006, 314(5803), pp. 1249-1250.

98 M. Boly, L. Tshibanda, A. Vanhaudenhuyse, Q. Noirhomme, C. Schnakers, D. Ledoux, P. Boveroux, C. Garweg, B. Lambermont, C. Phillips, A. Luxen, G. Moonen, C. Bassetti, P. Maquet et S. Laureys, « Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient », *Hum Brain Mapp*, 2009, 30(8), pp. 2393-2400 ; M.A. Bruno, A. Soddu,

du mode par défaut[99] a été observée chez des patients en état végétatif/non répondant. Récemment, nous avons pu démontrer qu'il existait une corrélation entre le niveau de connectivité au sein du réseau du mode par défaut et le degré de conscience des patients[100]. Spécifiquement, plus le niveau de conscience est bas chez ces patients (coma, état végétatif/non répondant), plus le degré de connectivité du réseau du mode par défaut diminue. De plus, la connectivité du cortex postérieur cingulaire/précunéus avec l'ensemble du réseau permet de différencier les patients en état végétatif/non répondant, des patients en état de conscience minimale[101], suggérant une relation étroite entre le niveau d'activité de cette région et le degré de conscience des patients. L'ensemble de ces études permet donc de confirmer le rôle du réseau du mode par défaut dans les processus de conscience.

5.2. *Paradigmes actifs : pouvoir communiquer sans parole ni geste ?*

Actuellement, pouvoir distinguer une activité cérébrale automatique d'une activité volontaire consciente reste encore difficile. Les paradigmes dits « actifs » permettent aux patients sévèrement cérébrolésés de démontrer et communiquer leur conscience par des canaux autres que les canaux classiques moteurs et langagiers. En 2006, Owen et *al*. ont proposé d'appliquer un paradigme actif en IRMf chez une patiente initialement diagnostiquée comme étant en état végétatif/non répondant[102]. Ils lui ont demandé de

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A. Demertzi, S. Laureys, O. Gosseries, C. Schnakers, M. Boly, Q. Noirhomme, M. Thonnard, C. Chatelle et A. Vanhaudenhuyse, « Disorders of consciousness : moving from passive to resting state and active paradigms », *Cognitive Neurosciences*, 2010a, 1(3), pp. 193-203.

99 M. Boly, L. Tshibanda, A. Vanhaudenhuyse, Q. Noirhomme, C. Schnakers, D. Ledoux, P. Boveroux, C. Garweg, B. Lambermont, C. Phillips, A. Luxen, G. Moonen, C. Bassetti, P. Maquet et S. Laureys, « Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient », *Hum Brain Mapp*, 2009, 30(8), pp. 2393-2400 ; F. Cauda, B.M. Micon, K. Sacco, S. Duca, F. D'Agata, G. Geminiani et S. Canavero, « Disrupted intrinsic functional connectivity in the vegetative state », *J Neurol Neurosurg Psychiatry*, 2009, 80(4), pp. 429-431.

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101 A. Vanhaudenhuyse, Q. Noirhomme, L.J. Tshibanda, M.A. Bruno, P. Boveroux, C. Schnakers, A. Soddu, V. Perlbarg, D. Ledoux, J.F. Brichant, G. Moonen, P. Maquet, M.D. Greicius, S. Laureys et M. Boly, « Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients », *Brain*, 2010b, 133(Pt 1), pp. 161-171.

102 A.M. Owen, M.R. Coleman, M. Boly, M.H. Davis, S. Laureys et J.D. Pickard, « Detecting awareness in the vegetative state », *Science*, 2006, 313(5792), pp. 1402.

Figure 3

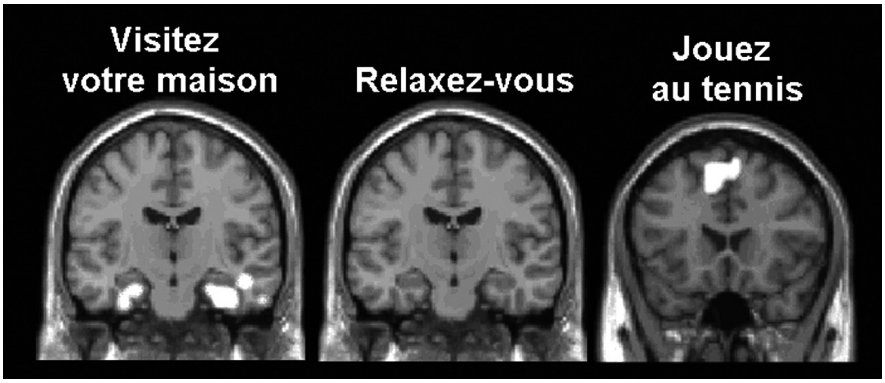


Illustration de l'activité cérébrale (en blanc) lors de 2 tâches d'imagerie motrice et spatiale.

réaliser deux tâches d'imagerie mentale (s'imaginer jouer au tennis et s'imaginer visiter sa maison), préalablement validées chez une série de volontaires sains[103]. Dans cette étude, la patiente a été capable de démontrer sa conscience en modulant activement son activité neuronale, c'est-à-dire en activant des régions similaires à celles observées chez des sujets sains contrôles lors des deux tâches proposées (activation de l'aire motrice supplémentaire pour la tâche motrice et activation des gyri parahippocampiques pour la tâche visuo-spatiale – Figure 3). Soulignons que ces activations ne pouvaient être interprétées que comme provenant d'une intention consciente de la part de la patiente puisque i) la seule différence entre les deux tâches proposées était la consigne donnée en début de séquence (« jouez au tennis » ou « visitez votre maison »), ii) cette activité cérébrale durait l'entièreté de chaque période durant laquelle la tâche lui était demandée (30 secondes), iii) l'activité était localisée dans les régions connues pour leur implication dans des tâches d'imagerie mentale et iv) elle perdurait jusqu'au moment où la patiente recevait une nouvelle consigne (« relaxez-vous »)[104]. Par la suite, ce

103 M. Boly, M.R. Coleman, M.H. Davis, A. Hampshire, D. Bor, G. Moonen, P.A. Maquet, J.D. Pickard, S. Laureys et A.M. Owen, « When thoughts become action : an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients », *Neuroimage*, 2007, 36(3), pp. 979-992.

104 A. M. Owen, M. Coleman, M. Boly, M. Davis, S. Laureys, J. Jolles et J. Pickard, « Response to Comments on « Detecting Awareness in the Vegetative State », *Science*, 2007, 315 (5816).

paradigme a été appliqué chez 54 patients en état de conscience altérée[105]. Parmi ces patients, 5 (2 en état végétatif/non répondant et 3 en état de conscience minimale) ont montré une activité consistante avec les tâches d'imagerie motrice et visuo-spatiale. Ce paradigme actif a ensuite été adapté en un système de communication par réponse oui/non, permettant ainsi à un patient en état de conscience minimale d'étiologie post-traumatique de communiquer sans avoir recours aux canaux classiques de communication[106]. Des outils autres que l'IRMf existent pour permettre à ces patients de démontrer et de communiquer leur conscience. Des interfaces cerveau/ordinateur (*Brain Computer Interfaces – BCI*) permettant un usage au quotidien sont de plus en plus développées actuellement[107]. Une BCI est un outil de communication qui permet à la personne d'envoyer un message ou une commande au monde extérieur sans avoir à passer par les processus nerveux périphériques et musculaires. Les patients atteints d'un *locked-in* syndrome complet (souvent observé en fin de sclérose latérale amyotrophique) sont incapables de communiquer par les voies traditionnelles verbales ou gestuelles, mais ils le peuvent par l'intermédiaire d'un système adapté en EEG[108]. Grâce à l'enregistrement électrœncéphalographique de potentiels évoqués lors de tâches actives similaires à celles appliquées en IRMf (par exemple : comptez le nombre de fois que vous entendez votre prénom), une activité cognitive consciente peut être détectée chez des patients sévèrement cérébrolésés incapables de communiquer[109]. Un autre exemple de BCI est le

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105 M.M. Monti, A. Vanhaudenhuyse, M.R. Coleman, M., Boly, J.D. Pickard, L. Tshibanda, A.M. Owen et S. Laureys, « Willful modulation of brain activity in disorders of consciousness », *N Engl J Med*, 2010, 362(7), pp. 579-589.

106 *Ibid.*

107 A. Kübler, « Brain-Computer Interfaces for Communication in Paralysed Patients and Implications for Disorders of Consciousness », *in The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 217-233.

108 N. Birbaumer, N. Ghanayim, T. Hinterberger, I. Iversen, B. Kotchoubey, A. Kübler, J. Perelmouter, E. Taub et H. Flor, « A spelling device for the paralysed », *Nature*, 1999, 398(6725), pp. 297-298 ; T. Hinterberger, B. Wilhelm, J. Mellinger, B. Kotchoubey et N. Birbaumer, « A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients », *IEEE Trans Biomed Eng*, 2005, 52(2), pp. 211-220 ; A. Kübler, « Brain-Computer Interfaces for Communication in Paralysed Patients and Implications for Disorders of Consciousness », *in The Neurology of Consciousness : Cognitive Neuroscience and Neuropathology*, sous la direction de S. Laureys et G. Tononi, Oxford, Elsevier, 2009, pp. 217-233.

109 C. Schnakers, F. Perrin, M. Schabus, S. Majerus, D. Ledoux, P. Damas, M. Boly, A. Vanhaudenhuyse, M.A. Bruno, G. Moonen et S. Laureys, « Voluntary brain processing in disorders of consciousness »,

système de manipulation mentale du pH salivaire[110], qui est également utilisé chez certains patients atteints du *locked-in* syndrome[111].

6. Traitements pharmacologiques et para-pharmacologiques

Aucune preuve suffisante ne supporte actuellement l'utilisation spécifique d'un agent pharmacologique pour augmenter l'éveil et restaurer la conscience chez les patients sévèrement cérébrolésés souffrant de troubles de la conscience. Malgré qu'aucun traitement ne se soit révélé suffisamment efficient pour être appliqué à la population générale de ces patients, une réponse clinique a toutefois été observée chez une minorité d'entre eux. En effet, des améliorations transitoires ou permanentes ont été observées chez certains patients en état végétatif/non répondant et en état de conscience minimale d'étiologies diverses. Les progrès observés sont variables selon les patients et le type de molécules administrées. Les traitements par amantadine, levodopa, bromocriptine, apomorphine, méthyphénidate, zolpidem, baclofène, sertaline, amitriptyline, désipramine ou encore par lamotrigine ont montré des améliorations chez certains patients telles qu'une augmentation de l'éveil, un regain de conscience partielle ou totale, une amélioration motrice, verbale, cognitive ou encore une récupération d'une communication fonctionnelle ou d'une interaction gestuelle[112]. Certains de ces traitements semblent inciter directement à une restauration de la conscience (par exemple : amantadine, zolpidem, baclofène), alors que d'autres (par exemple : méthylphénidate, lamotrigine) jouent un rôle plus déterminant dans l'amélioration des domaines cognitifs, surtout chez les patients conscients mais souffrant toujours de troubles cognitifs sévères de l'attention ou de la vigilance[113]. Des

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Neurology, 2008c, 71, pp. 1614-1620 ; C. Schnakers, F. Perrin, M. Schabus, R. Hustinx, S. Majerus, G. Moonen, M. Boly, A. Vanhaudenhuyse, M.A. Bruno et S. Laureys, « Detecting consciousness in a total locked-in syndrome : An active event-related paradigm », *Neurocase*, 2009a, pp. 1-7.

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111 B. Wilhelm, M. Jordan et N. Birbaumer, *Communication in locked-in syndrome : Effects of imagery on salivary pH*, 2006, 67, pp. 534-535.

112 Pour une revue, voy. O. Gosseries, M. Thonnard et S. Laureys, « Les traitements pharmacologiques chez les patients récupérant du coma », *in Coma et états de conscience altérée*, sous la direction de C. Schnakers et S. Laureys, Paris, Springer-Verlag, 2011.

113 F. Pistoia, E. Mura, S. Govoni, M. Fini et M. Sarà, « Awakenings and awareness recovery in disorders of consciousness : is there a role for drugs ? », *CNS Drugs*, 2010, 24(8), pp. 625-638.

effets ont été observés à court terme et à long terme, et ce, découlant d'une dose unique (par exemple : zolpidem) ou d'un traitement en continu (par exemple : amantadine, baclofène ou levodopa).

À ce jour, les preuves ne sont cependant pas suffisantes pour orienter la pratique clinique et diriger la prise en charge de ces patients. En effet, les données proviennent principalement de rapports de cas ou d'études présentant des limitations méthodologiques. La plupart des études ne comportent également que peu de sujets et ne sont pas basées sur un protocole de recherche clinique rigoureux. Les études comprenant un large nombre de patients sont partiellement biaisées par l'extrême hétérogénéité des patients quant aux lésions neuropathologiques, au délai entre la lésion et l'instauration du traitement, à l'évolution clinique personnelle et aux comorbidités médicales. De plus, il est difficile de comparer les études entre elles puisqu'elles manquent d'homogénéité et diffèrent par la durée de leur traitement, les doses administrées, l'étiologie des patients, etc. De toute évidence, un plus grand nombre d'études multicentriques standardisées, contrôlées, randomisées, en double aveugle et comprenant un grand nombre de patients sont nécessaires avant de pouvoir tirer des conclusions sur l'efficacité des traitements pharmacologiques. Les interventions non pharmacologiques, complémentaires et essentielles à la prise en charge des patients en état de conscience altérée, comprennent principalement la revalidation physique et cognitive ainsi que des programmes de stimulations sensorielles. La stimulation cérébrale profonde reste quant à elle encore du registre expérimental, mais a montré certains effets positifs sur la reprise de conscience chez des patients sévèrement cérébrolésés[114].

7. Conclusion

Émettre un diagnostic d'état de conscience altérée est primordial afin de permettre aux équipes médicales d'adapter le traitement et de prendre des décisions adéquates quant à la revalidation des patients sévèrement cérébrolésés. Actuellement, les évaluations comportementales sont parfois difficiles à interpréter quant à la signification de certains comportements en termes de

[114] N.D. Schiff, J.T. Giacino, K. Kalmar, J.D. Victor, K. Baker, M. Gerber, B. Fritz, B. Eisenberg, T. Biondi, J. O'Connor, E.J. Kobylarz, S. Farris, A. Machado, C. McCagg, F. Plum, J.J. Fins et A.R. Rezai, « Behavioural improvements with thalamic stimulation after severe traumatic brain injury », *Nature*, 2007, 448(7153), pp. 600-603.

conscience. Ces limites engendrent la nécessité de faire appel à des experts pour émettre un diagnostic fiable d'état de conscience altérée. Dès lors, nous travaillons en parallèle avec d'autres mesures plus objectives de détection de la conscience, telles que la TEP, l'IRMf et l'EEG. Les différents travaux présentés dans ce chapitre démontrent l'intérêt de ces techniques comme outils d'aide au diagnostic d'état de conscience altérée. Les paradigmes au repos ainsi que les tâches actives permettent de détecter une conscience résiduelle et une relative préservation des fonctions cognitives chez ces patients incapables de communiquer et parfois même incapables de démontrer cliniquement leur conscience. La TEP permet de mettre en évidence les régions cérébrales préservées, tandis que l'IRMf permet d'identifier si ces régions sont fonctionnellement connectées entre elles. Par la combinaison de ces deux techniques, une information plus précise sur la fonctionnalité corticale et sous-corticale pourrait être obtenue permettant de la sorte d'affiner davantage le diagnostic d'état de conscience altérée. Nous avons également démontré la possibilité d'établir une communication de base grâce aux paradigmes actifs en IRMf. Malheureusement, cette technique est peu pratique au quotidien. C'est pourquoi d'autres méthodes, similaires, sont développées via des interfaces cerveau-ordinateur. Enfin, même si aucune généralisation ne peut être faite par rapport aux traitements pharmacologiques et non pharmacologiques, ceux-ci peuvent être efficaces dans le cas de certains patients et valent donc la peine d'être envisagés.

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CHAPTER

15

Consciousness in the Locked-in Syndrome

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OUTLINE

Definition	**192**
Aetiology	**192**
Misdiagnosis	**192**
Survival And Mortality	**193**
Prognosis And Outcome	**194**
Communication	**195**
Residual Brain Function	**195**
Neuropsychological Testing	*195*
Electrophysiologic Measurements	*197*
Functional Neuroimaging	*198*
Daily Activities	**199**
Quality Of Life	**199**
The Right To Die Or The Right To Live?	**199**
Conclusion	**200**
Acknowledgements	**201**
References	*201*

ABSTRACT

Patients in a locked-in syndrome (LIS) are selectively deefferented, that is, have no means of producing speech, limb, or face movements. Usually the anatomy of the responsible lesion in the brainstem is such that locked-in patients are left with the capacity to use vertical eye movements and blinking to communicate their awareness. The syndrome is subdivided as: (a) *classical* LIS is characterized by total immobility except for vertical eye movements or blinking; (b) *incomplete* LIS permits remnants of voluntary motion; and (c) *total* LIS with complete immobility including all eye movements combined with preserved consciousness. Eye-controlled computer-based communication technology currently allows these patients to control their environment, use a word processor coupled to a speech synthesizer and access the worldwide net.

'Thirty years ago a stroke left me in a coma. When I awoke I found myself completely paralyzed and unable to speak… I didn't know what paralysis was until I could move nothing but my eyes. I didn't know what loneliness was until I had to wait all night in the dark, in pain from head to foot, vainly hoping for someone to come with a teardrop of comfort. I didn't know what silence was until the only sound I could make was that of my own breath issuing from a hole drilled into my throat' [1].

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DEFINITION

Plum and Posner first introduced the term 'locked-in syndrome' (LIS) in 1966 referring to the constellation of quadriplegia and anarthria brought about by the disruption of the brainstem's corticospinal and corticobulbar pathways, respectively [2]. In the LIS, unlike coma, the vegetative state or akinetic mutism, consciousness remains intact. The patient is locked inside his body, able to perceive his environment but extremely limited to voluntarily interact with it.

The American Congress of Rehabilitation Medicine most recently defined LIS by (i) the presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor); (ii) preserved basic cognitive abilities; (iii) aphonia or severe hypophonia; (iv) quadriplegia or quadriparesis; and (v) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid [3].

Bauer *et al*. [4] subdivided the syndrome on the basis of the extent of motor and verbal impairment: (a) *classical* LIS is characterized by total immobility except for vertical eye movements or blinking; (b) *incomplete* LIS permits remnants of voluntary motion; and (c) *total* LIS consists of complete immobility including all eye movements combined with preserved consciousness.

AETIOLOGY

LIS is most frequently caused by a bilateral ventral pontine lesion (e.g., [2, 5]) (Figure 15.1). In rarer instances, it can be the result of a mesencephalic lesion (e.g., [4, 6, 7]). The most common aetiology of LIS is vascular pathology, either a basilar artery occlusion or a pontine haemorrhage [8]. Another relatively frequent cause is traumatic brain injury [9–14]. Following trauma, LIS may be caused either directly by brainstem lesions, secondary to vertebral artery damage and vertebrobasilar arterial occlusion, or to compression of the cerebral peduncles from tentorial herniation [13]. It has also been reported secondary to subarachnoid haemorrhage and vascular spasm of the basilar artery, a brainstem tumour, central pontine myelinolysis, encephalitis, pontine abscess, brainstem drug toxicity, vaccine reaction, and prolonged hypoglycemia [8].

A comparable awake conscious state simulating unresponsiveness may also occur in severe cases of peripheral polyneuropathy as a result of total paralysis of limb, bulbar, and ocular musculature. Transient LIS cases have been reported after Guillain-Barré polyradiculoneuropathy [15–17] and severe post-infectious polyneuropathy [18, 19]. Unlike basilar artery stroke,

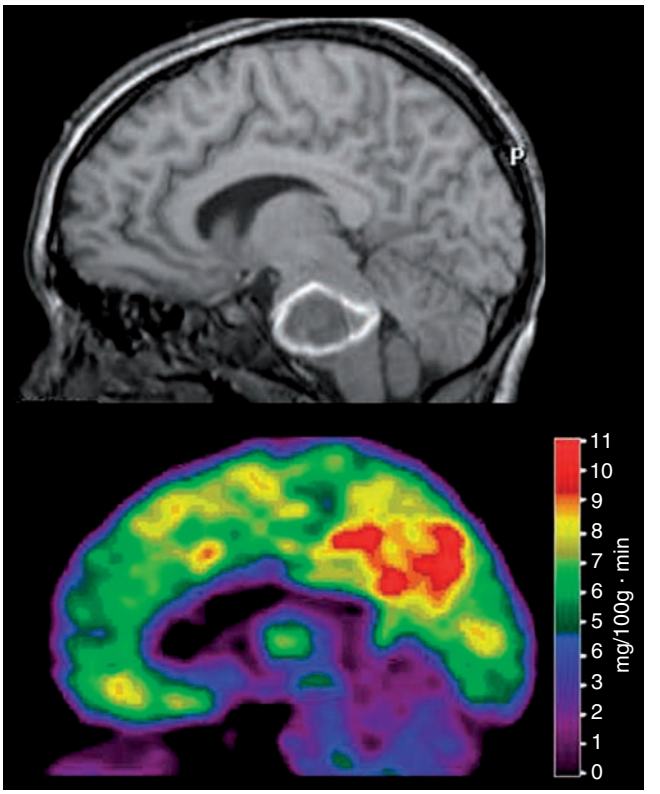


FIGURE 15.1 Upper panel: Magnetic resonance image (sagittal section) showing a massive hemorrhage in the brainstem (circular hyperintensity) causing LIS in a 13-year old girl. Lower panel: ^{18}F-fluorodeoxyglucose-Positron Emission Tomography illustrating intact cerebral metabolism in the acute phase of the LIS when eye-coded communication was difficult due to fluctuating vigilance. The colour scale shows the amount of glucose metabolized per 100 g of brain tissue per minute. Statistical analysis revealed that metabolism in the supra-tentorial gray matter was not significantly lower as compared to healthy controls (taken from Laureys *et al*., [8]).

vertical eye movements are not selectively spared in these extensive peripheral disconnection syndromes. Another important cause of complete LIS can be observed in end-stage amyotrophic lateral sclerosis, that is, motor neuron disease [20–22]. Finally, temporary pharmacologically induced LIS can sporadically be observed in general anaesthesia when patients receive muscle relaxants together with inadequate amounts of anaesthetic drugs (e.g., [23]). Testimonies from victims relate that the worst aspect of the experience was the anxious desire to move or speak while being unable to do so [24–26]. Awake-paralyzed patients undergoing surgery may develop post-traumatic stress disorder (for recent review, see [27]).

MISDIAGNOSIS

Unless the physician is familiar with the signs and symptoms of the LIS, the diagnosis may be missed

BOX 15.1

FAMOUS LOCKED-IN PATIENTS

The LIS first described in Alexandre Dumas's novel the Count of Monte Cristo (1844–1845) [28]. Herein, Monsieur Noirtier de Villefort, was depicted as 'a corpse with living eyes'. Mr. Noirtier had been in this state for more than 6 years, and he could only communicate by blinking his eyes. His helper pointed at words in a dictionary and the monsignor indicated with his eyes the words he wanted. Some years later, Emile Zola wrote in his novel Thérèse Raquin [29] (1868) about a paralyzed woman who 'was buried alive in a dead body' and 'had language only in her eyes'. Dumas and Zola highlighted the locked-in condition before the medical community did.

For a long time, LIS has mainly been a retrospective diagnosis based on post-mortem findings [5, 30]. Medical technology now can achieve long survival in such cases – the longest history of this condition being 29 years (French ALIS). Computerized devices now allow the LIS patient and other patients with severe motor impairment to 'speak'. The preeminent physicist Stephen Hawking, author of the best-sellers *A Brief History of Time* and *The Universe in a Nutshell*, is able to communicate solely through the use of a computerized voice synthesizer. With one finger, he selects words presented serially on a computer screen; the words are then stored and later presented as a synthesized and coherent message (http://www.hawking.org.uk). The continuing brilliant productivity of Hawking despite his failure to move or speak illustrates that locked-in patients can be productive members of the society.

In December 1995, Jean-Dominique Bauby, aged 43 and editor-in-chief of the fashion magazine 'Elle', had a brainstem stroke. He emerged from a coma several weeks later to find himself in a LIS only able to move his left eyelid and with very little hope of recovery. Bauby wanted to show the world that this pathology, which impedes movement and speech, does not prevent patients from living. He has proven it in an extraordinary book in which he composed each passage mentally and then dictated it, letter by letter, to an amanuensis who painstakingly recited a frequency-ordered alphabet until Bauby chose a letter by blinking his left eyelid once to signify 'yes'. His book [31] *The diving bell and the butterfly* became a best-seller only weeks after his death due to septic shock on March 9, 1997. Bauby created an ALIS aimed to help patients with this condition and their families (http://www.alis-asso.fr).

Since its creation in 1997, ALIS has registered 438 locked-in patients in France (situation in May 2007).

and the patient may erroneously be considered as being in a coma, vegetative state, or akinetic mutism [32]. In a recent survey in 44 LIS patients belonging to the French Association for Locked-in Syndrome (ALIS, see Box 15.1) the first person to realize the patient was conscious and could communicate via eye movements most often was a family member (55% of cases) and not the treating physician (23% of cases) [33]. Most distressingly, the time elapsed between brain insult and LIS diagnosis was on an average of 2.5 months (78 days). Several patients were not diagnosed for more than 4 years. Leon-Carrion *et al*. [33] believed that this delay in the diagnosis of LIS mainly reflected initial misdiagnosis. Clinical experience indeed shows how difficult it is to recognize unambiguous signs of conscious perception of the environment and of the self in severely brain-injured patients. Voluntary eye movements and/or blinking can erroneously be interpreted as reflexive in anarthric and nearly completely paralyzed patients who classically show decerebration posturing (i.e., stereotyped extension reflexes). However, part of the delay could be explained by an initial lower level neurological state (e.g., decreased or fluctuating arousal levels) or even psychiatric symptoms which would mask residual cognitive functions at the outset of LIS.

SURVIVAL AND MORTALITY

It has been stated that long-term survival in LIS is rare [34]. Mortality is indeed high in acute LIS (76% for vascular cases and 41% for non-vascular cases) with 87% of the deaths occurring in the first 4 months [5]. In 1987, Haig *et al*. first [35] reported on the life expectancy of persons with LIS, showing that individuals can actually survive for significant periods of time. Encompassing 29 patients from a major US rehabilitation hospital who had been in a LIS for more than 1 year they reported formal survival curves at 5-year [36] and 10-year follow-up [37]. These authors

have shown that once a patient has medically stabilized in LIS for more than a year, 10-year survival is 83% and 20-year survival is 40% [37].

Data from the ALIS database ($n = 320$) show that survivors are younger at onset than those who die (Figure 15.2). The mean time spent in locked-in is 6 ± 4 years (range 14 days to 29 years, the latter patient still being alive). Reported causes of death for the 42 deceased subjects are predominantly infectious (40%, most frequently pneumonia), primary brainstem stroke (25%), recurrent brainstem stroke (10%), patient's refusal of artificial nutrition and hydration (10%), and other causes (i.e., cardiac arrest, gastrostomy surgery, heart failure, and hepatitis). It should be noted that the ALIS database does not contain the many LIS patients who die in the acute setting without being reported to the association. Recruitment of the ALIS database is based on case reporting by family and health care workers prompted by the exceptional media publicity of ALIS in France and tracked by continuing yearly surveys. This recruitment bias should, however, be taken into account when interpreting the presented data.

PROGNOSIS AND OUTCOME

Classically, the motor recovery of LIS of vascular origin is very limited [5, 37] even if rare cases of good recovery have been reported [38, 39]. Chang and Morariu [40] reported the first transient LIS caused by a traumatic damage of the brainstem. In their milestone paper, Patterson and Grabois [5], reviewed 139 patients – 6 cases from the author's rehabilitation centre in Texas, USA and 133 taken from 71 published studies from 1959 to 1983 and reported earlier and more complete recovery in non-vascular LIS compared to vascular LIS. Return of horizontal pursuit eye movements within 4 weeks post-onset are thought to be predictive of good recovery [6]. Richard *et al*. [41] followed 11 LIS patients for 7 months to 10 years and observed that despite the persisting serious motor deficit, all patients did recover some distal control of fingers and toe movements, often allowing a functional use of a digital switch. The motor improvement occurred with a distal to proximal progression and included a striking axial hypotonia.

LIS is uncommon enough that many clinicians do not know how to approach rehabilitation and there are no existing guidelines as how to organize the revalidation process. Casanova *et al*. [42] recently followed 14 LIS patients in three Italian rehabilitation centres for a period of 5 months to 6 years. They reported that intensive and early rehabilitative care improved functional outcome and reduced mortality rate when compared to the older studies by Patterson and Grabois [5] and Haig *et al*. [35].

Often unknown to physicians caring for LIS in the acute setting and despite the limited motor recovery of LIS patients, many patients can return living at home. The ALIS database shows that out of 245 patients, 108

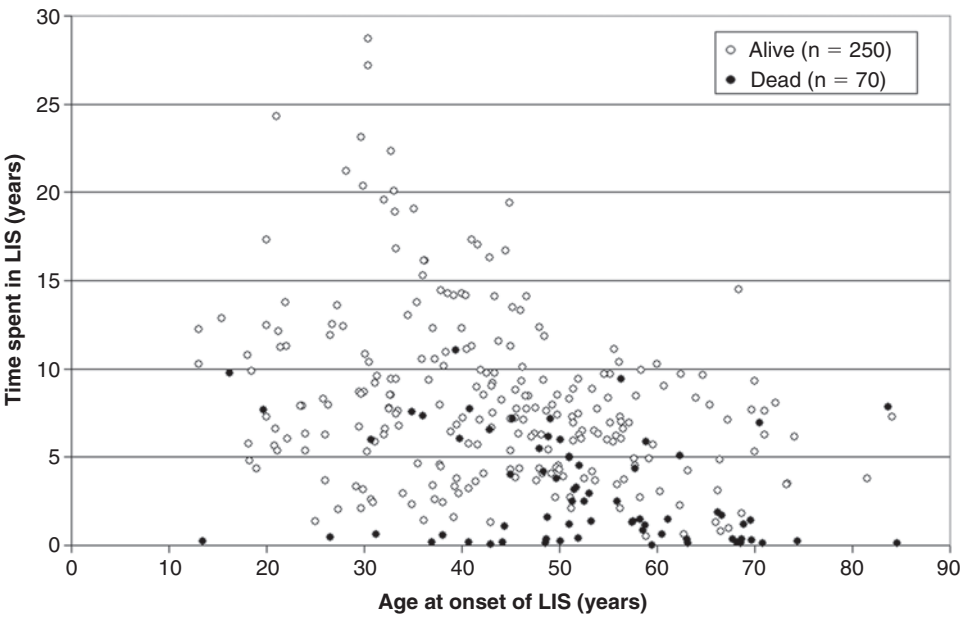


FIGURE 15.2 Age at insult vs. survival time of 320 locked-in patients registered in the ALIS database, 70 of whom died (filled circles).

(44%) are known to live at home (21% are staying in a hospital setting and 17% in a revalidation centre). Patients return home after a mean period of 2±16 years (range 2 months to 6 years, data obtained on $n = 55$). Results obtained in 95 patients show a moderate to significant recovery of head movement in 92% of patients, 65% showed small movement in one of the upper limbs (finger, hand, or arm) and 74% show a small movement in lower limbs (foot or leg). Half of the patients has recovered some speech production (limited to single comprehensible words) and 95% can vocalize unintelligible sounds (data obtained on $n = 50$). Some kind of electrical communication device is used by 81% of the LIS patients (data obtained on $n = 95$) [8].

COMMUNICATION

In order to functionally communicate, it is necessary for the LIS patient to be motivated and to be able to receive (verbally or visually; i.e., written commands) and emit information. The first contact to be made with these patients is through a code using eyelid blinks or vertical eye movements. In cases of bilateral ptosis the eyelids need to be manually opened in order to verify voluntary eye movements on command. To establish a yes/no eye code, the following instruction can suffice: 'yes' is indicated by one blink and 'no' by two or look indicates 'yes' and look down 'no'. In practice, the patient's best eye movement should be chosen and the same eye code should be used by all interlocutors. Such a code will only permit to communicate via closed questions (i.e., yes/no answers on presented questions). The principal aim of reeducation is to reestablish a genuine exchange with the LIS patient by putting into place various codes to permit them to reach a higher level of communication and thus to achieve an active participation. With sufficient practice, it is possible for LIS patients to communicate complex ideas in coded eye movements. Feldman [43] has first described a LIS patient who used jaw and eyelid movements to communicate in Morse Code.

Most frequently used are alphabetical communication systems. The simplest way is to list the alphabet and ask the LIS patient to make a pre-arranged eye movement to indicate a letter. Some patients prefer a listing of the letters sorted in function of appearance rate in usual language (i.e., in the English language: E-T-A-O-I-N-S-R-H-L-D-C-U-M-F-P-G-W-Y-B-V-K-X-J-Q-Z). The interlocutor pronounces the letters beginning with the most frequently used, E, and continues until the patient blinks after hearing the desired letter which the interlocutor then notes. It is necessary to begin over again for each letter to form words and phrases. The rapidity of this system depends upon practice and the ability of patient and interlocutor to work together. The interlocutor may be able to guess at a word or a phrase before all the letters have been pronounced. It is sufficient for him to pronounce the word or the rest of the sentence. The patient than confirms the word by making his eye code for 'yes' or disproves by making his eye code for 'no'. Other systems have been discussed elsewhere [8].

The above discussed communication systems all require assistance from others. Recent developments in informatics are drastically changing the lives of patients with LIS. Instead of passively responding to the requests of others, new communication facilitation devices couplet to computers now allow the patient to initiate conversations [8]. Experts in rehabilitation engineering and speech-language pathology are continuingly improving various brain–computer interfaces (BCI). BCIs (also named thought translation devices) are a mean of communication in which messages or commands that an individual sends to the external world do not pass through the brain's normal output pathways of peripheral nerves and muscles [44]. These patient–computer interfaces such as infrared eye movement sensors which can be coupled to on-screen virtual keyboards allowing the LIS survivor to control his environment, use a word processor (which can be coupled to a text-to-speech synthesizer), operate a telephone of fax, or access the Internet and use e-mail (Figure 15.3; Box 15.2).

Wilhelm *et al*. [45] have shown that mental manipulation of salivary *p*H may be an alternative way to document consciousness in acute LIS (see Figure 15.4). Birbaumer *et al*. [46] reported that chronic near-complete LIS and end-stage amyotrophic lateral sclerosis, patients were able to communicate without any verbal or motor report but solely by modulating their electroencephalographic (EEG). In the future, more widely available access to enhanced communication computer prosthetics should additionally enhance the quality of life of LIS survivors (also see Chapter 17).

RESIDUAL BRAIN FUNCTION

Neuropsychological Testing

Surprisingly, there are no systematic neuropsychological studies of the cognitive functions in patients living with a LIS. Most case reports, however, failed to show any significant cognitive impairment when LIS patients were tested 1 year or more after the brainstem

BOX 15.2

TESTIMONIES WRITTEN BY LIS SURVIVORS

Some memoirs written by LIS patients well illustrate the clinical challenge of recognizing a LIS. A striking example is *Look Up for Yes* written by Julia Tavalaro [1]. In 1966, 32-year old Tavalaro fell into a coma following a subarachnoid hemorrhage. She remained in a coma for 7 months and gradually woke up to find herself in a New York State chronic care facility. There, she was known as 'the vegetable' and it was not until 1973 (i.e., after 6 years) that her family identified a voluntary 'attempt to smile' when Julia was told a dirty joke. This made speech therapist Arlene Kraat brake through Julia's isolation. With the speech therapist pointing to each letter on a letter board, Julia began to use her eyes to spell out her thoughts and relate the turmoil of her terrible years in captivity. She later used a communication device, started to write poetry and could cheek-control her wheelchair around the hospital. Julia Tavalaro died in 2003 at age 68 from aspiration pneumonia.

Another poignant testimony comes from Philippe Vigand, author of *Only the Eyes Say Yes* (original publication in 1997) and formerly publishing executive with the French conglomerate Hachette. The book is written in two parts, the first by Philippe, the second by his wife Stéphane detailing *her* experiences. In 1990, Philippe Vigand, 32-years old, presented a vertebral artery dissection and remained in a coma for 2 months. Philippe and his wife write that at first, doctors believed he was a 'vegetable and was treated as such'. His wife eventually realized that he was blinking his eyes in response to her comments and questions to him but had difficulties convincing the treating physicians. It was speech therapist Philippe Van Eeckhout who formally made the diagnosis of LIS: when testing Vigand's gag reflex, Van Eeckhout was bit in his finger and yelled 'chameau' (French for 'camel'), whereupon the patient started to grin. On the subsequent question 'how much is 2 plus 2' Vigand blinked four times confirming his cognitive capacities. He later communicated his first phrase by means of a letter board: 'my feet hurt'. After many months of hospital care, Vigand was brought home, where an infrared camera attached to a computer enabled him to 'speak'. The couple conceived a child after Philippe became paralyzed and he has written his second book (dealing with the menaced French ecosystem) on the beach of the Martinique isles [47] illustrating that LIS patients can resume a significant role in family and society.



FIGURE 15.3 A locked-in person updates the database of ALIS, moving the cursor on screen by eye movements. An infrared camera (white arrow) mounted below the monitor observes one of the user's eyes, an image processing software continually analyzes the video image of the eye and determines where the user is looking on the screen. The user looks at a virtual keyboard that is displayed on the monitor and uses his eye as a computer-mouse. To 'click' he looks at the key for a specified period of time (typically a fraction of a second) or blinks. An array of menu keys allow the user to control his environment, use a speech synthesizer, browse the worldwide web or send e-mail independently (picture used with kind permission from DT).With a similar device Philippe Vigand, locked-in since 1990, has written a testimony of his LIS experience in an astonishing book 'Putain de silence' translated as 'Only the eyes say yes' [48].

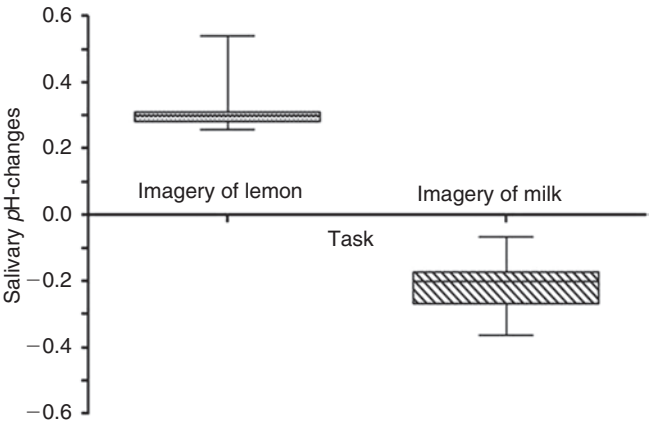


FIGURE 15.4 Communication method based on mental imagery and measurement of salivary *p*H changes. Imagery of lemon increases salivary *p*H and is used to communicate 'yes' while imagery of milk decreases *p*H and communicates 'no'. Result obtained in one healthy volunteer box and whiskers represent mean, SD and minimum/maximum measurements. *Source*: Adapted from Vanhaudenhuyse *et al*. [49].

insult. Allain *et al*. [50] performed extensive neuropsychological testing in two LIS patients studied 2 and 3 years after their basilar artery thrombosis. Patients communicated via a communication PrintWriter system and showed no impairment of language, memory, and intellectual functioning. Cappa *et al*. [51, 52] studied one patient who was LIS for over 12 years and observed intact performances on language, calculation, spatial orientation, right–left discrimination, and personality testing. Recently, New and Thomas [53] assessed cognitive functioning in a LIS patient 6 months after basilar artery occlusion and noted significant reduction in speed of processing, moderate impairment of perceptual organization and executive skills, mild difficulties with attention, concentration, and new learning of verbal information. Interestingly, they subsequently observed progressive improvement in most areas of cognitive functioning until over 2 years after his brainstem stroke.

In a survey conducted by ALIS and Léon-Carrion *et al*. [33] in 44 chronic LIS patients, 86% reported a good attentional level, all but two patients could watch and follow a film on TV and all but one were well-oriented in time (mean duration of LIS was 5 years). More recently, ALIS and Schnakers *et al*. [54] adapted a standard battery of neuropsychological testing (i.e., sustained and selective attention, working and episodic memory, executive functioning, phonological and lexico-semantic processing and vocabulary knowledge) to an eye-response mode for specific use in LIS patients. Overall, performances in the LIS patients studied 3 to 6 years after their brainstem insult were not significantly different from matched healthy controls who, like the LIS patients, had to respond solely via eye movements (Figure 15.5). These data re-emphasize the fact that LIS due to purely pontine lesions is characterized by the restoration of a globally intact cognitive potential.

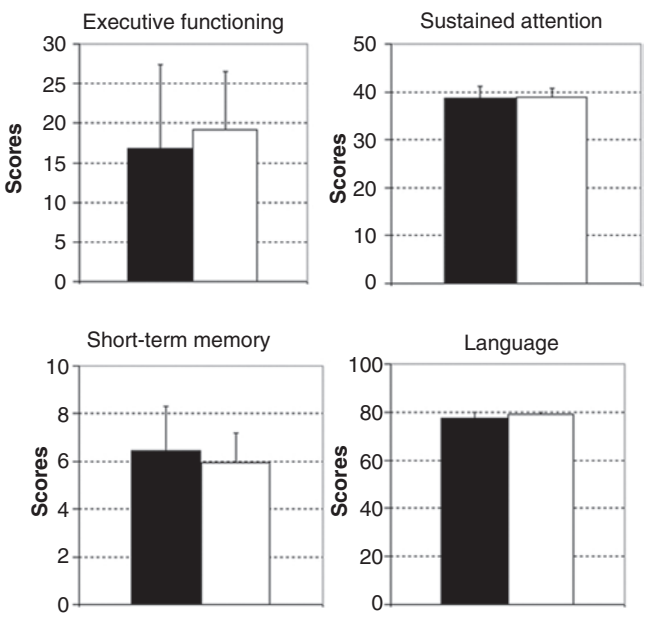


FIGURE 15.5 Neuropsychological testing data from six LIS patients (three males; mean age 42 ± 16 years) and 40 healthy adults (matched according to age and level of education). Note that LIS patients show cognitive functioning not significantly different from controls. *Source*: Data adapted from Schnakers *et al*. [54].

Electrophysiologic Measurements

Markland [55] reviewed EEG recordings in eight patients with LIS and reported it was normal or minimally slow in seven and showed reactivity to external stimuli in all patients. These results were confirmed by Bassetti *et al*. [56] who observed a predominance of reactive alpha activity in six LIS patients. In their seminal paper, Patterson and Grabois [5] reported normal EEG findings in 39 (45%) and abnormal (mostly slowing over the temporal or frontal leads or more diffuse slowing) in 48 (55%) patients out of 87 reviewed patients. Jacome and Morilla-Pastor [57], however, reported three patients with acute brainstem strokes and LIS whose repeated EEG recordings exhibited an 'alpha coma' pattern including an unreactive alpha rhythm to multimodal stimuli. Unreactive EEG in LIS was also reported by Gutling *et al*. [58] confirming that lack of alpha reactivity is not a reliable indicator of unconsciousness and cannot be used to distinguish the 'locked-in' patients from those comatose due to a brainstem lesion. Nevertheless, the presence of a relatively normal reactive EEG rhythm in a patient that appears to be unconscious should alert one to the possibility of a LIS.

Somatosensory evoked potentials are known to be unreliable predictors of prognosis [56, 59] but motor evoked potentials have been proposed to evaluate the potential motor recovery (e.g., [56]).

Cognitive event-related potentials (ERPs) in patients with LIS may have a role in differential diagnosis of brainstem lesions [60] and have also shown their utility to document consciousness in total LIS due to end-stage amyotrophic lateral sclerosis [22] and fulminant Guillain-Barré syndrome [16]. Figure 15.6 shows ERPs in locked-in patients showing a positive 'P3' component only evoked by the patient's own name (thick line) and not by other names (thin line). It should, however, be noted that such responses can also be evoked in minimally conscious patients [61]

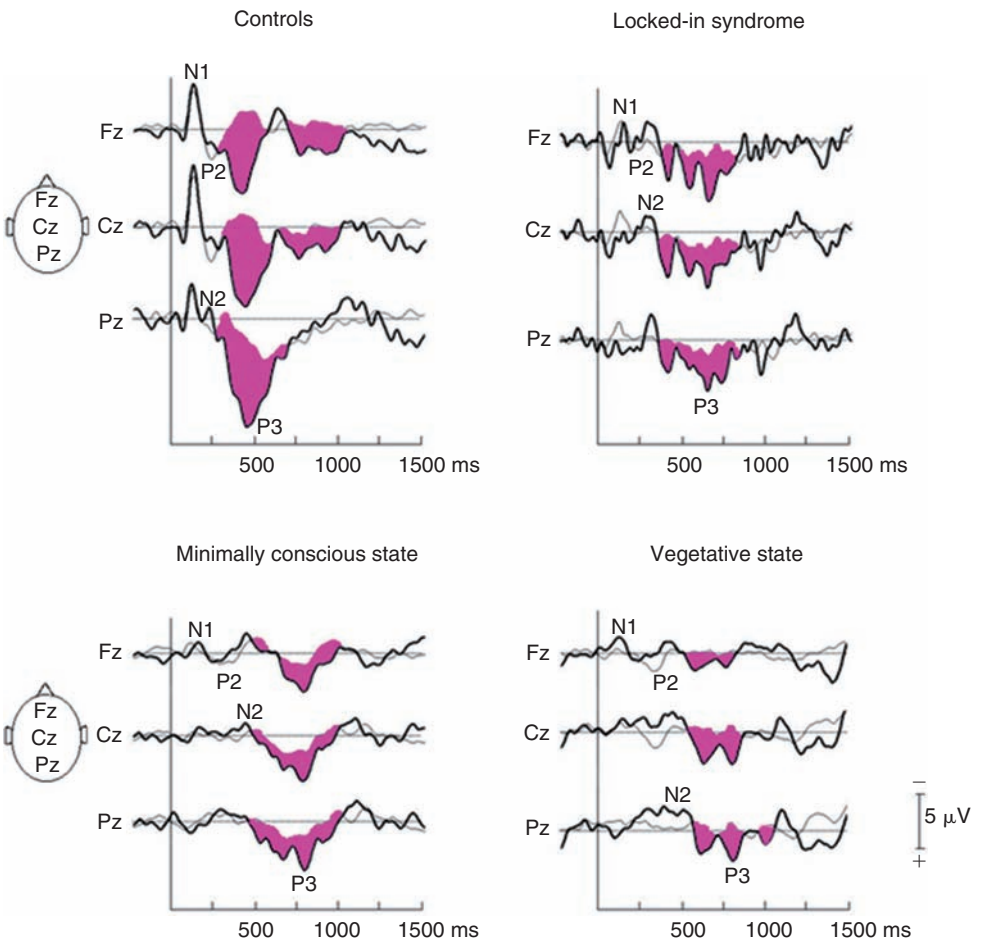


FIGURE 15.6 ERPs to the subject's own name (thick traces) and to other first names (thin traces) in controls ($n = 5$), LIS ($n = 4$), minimally conscious state ($n = 6$) and vegetative state ($n = 5$) patients. Note that a P3 response (pink) is no reliable marker of consciousness as it could be obtained in well-documented vegetative patients who never recovered. *Source*: Adapted from Perrin *et al*. [69].

and that they even persist in the vegetative state [62] and sleeping normal subjects [63].

Functional Neuroimaging

Classically, structural brain imaging (MRI) may show isolated lesions (bilateral infarction, haemorrhage, or tumour) of the ventral portion of the basis pontis or midbrain (e.g., [64]). PET scanning has shown significantly higher metabolic levels in the brains of patients in a LIS compared to patients in the vegetative state [65]. Preliminary results PET studies [66, 67] indicate that no supra-tentorial cortical area show significantly lower metabolism in acute and chronic LIS patients when compared to age-matched healthy controls (Figure 15.2). Conversely, a significantly hyperactivity was observed in bilateral amygdala of acute, but not chronic, LIS patients [8]. The absence of metabolic signs of reduced function in any area of the gray matter re-emphasizes the fact that LIS patients suffer from a pure motor deefferentation and recover an entirely intact intellectual capacity. Previous PET studies in normal volunteers have demonstrated amygdala activation in relation to negative emotions such as fear and anxiety (e.g., [69]). It is difficult to make judgments about patient's thoughts and feelings when they awake from their coma in a motionless shell. However, in the absence of decreased neural activity in any cortical region, we assume that the increased activity in the amygdala in acute non-communicative LIS patients, relates to the terrifying situation of an intact awareness in a sensitive being, experiencing frustration, stress and anguish, locked in an immobile body. These preliminary findings emphasize the need to quickly make the diagnosis and also recognize the terrifying situation of a pseudocoma (i.e., LIS) at the intensive care or coma unit. Health care workers should adapt their bedside-behaviour and consider pharmacological anxiolytic therapy of locked-in

patients, taking into account the intense emotional state they go through.

DAILY ACTIVITIES

For those not dealing with these patients on a daily basis it is surprising to see how chronic LIS patients, with the help of family and friends, still have essential social interaction and lead meaningful lives. Doble *et al*. [37] reported that most of their chronic LIS patients continued to remain active through eye and facial movements. Listed activities included: TV, radio, music, books on tape, visiting with family, visit vacation home, e-mail, telephone, teaching, movies, shows, the beach, bars, school, and vocational training. They also reported an attorney who uses Morse code eye blinks to provide legal opinions and keeps up with colleagues through fax and e-mail. Another patient teached math and spelling to third graders using a mouth stick to trigger an electronic voice device. The authors reported being impressed with the social interactions of chronic LIS patients and stated it was apparent that the patients were actively involved in family and personal decisions and that their presence was valued at home. Only four out of the 13 patients used computers consistently, two accessed the internet and one was able to complete the telephone interview by himself using a computer and voice synthesizer. A survey by ALIS showed that out of 17 questioned chronic LIS patients living at home, 11 (65%) used a personal computer [8].

QUALITY OF LIFE

A study conducted by the French ALIS assessed the quality of life in LIS. Chronic LIS survivors ($n = 17$, LIS duration 6 ± 4 years) who did not show major motor recovery (i.e., used eye movements or blinking as the major mode of communication) and who lived at home were asked to fill in the Short Form-36 (SF-36) questionnaire [70] on quality of life. On the basis of this questionnaire LIS patients unsurprisingly showed maximal limitations in physical activities (all patients scoring zero). Interestingly, self-scored perception of mental health (evaluating mental well-being and psychological distress) and personal general health were not significantly lower than values from age-matched French control subjects [8, 71]. Note that the perception of mental health and the presence of physical pain was correlated to the frequency of suicidal thought [8]. This stresses the importance of managing pain in chronic LIS patients. Our results confirm earlier reports on quality of life assessments in chronic LIS patients. Leon-Carrion *et al*. [33] and the French ALIS showed that about half of the assessed patients ($n = 44$) regarded their mood as good. Similarly, Doble *et al*. [37] studied 13 LIS patients and reported that more than half note were satisfied with life in general. In 2007, we have assessed the quality of life of 11 patients (LIS duration 7 ± 3 years) (unpublished data) using the ACSA scale (Anamnestic Comparative Self Assessment) [72]. ACSA estimates overall well-being on a scale from -5 (worst period in the respondent's life) to $+5$ (best period). As show in Figure 15.7, LIS patients' overall quality of life was not significantly different from healthy matched controls.

THE RIGHT TO DIE OR THE RIGHT TO LIVE?

As stated by The American Academy of Neurology (AAN), patients with profound and permanent paralysis have the right to make health care decisions about themselves including to accept or refuse life-sustaining therapy [73]. Bruno *et al*. have questioned 97 clinicians: At the affirmation: '*Being LIS is worse than being in a vegetative state or in a minimally conscious state*?', 66% said 'yes', 34% 'no' [74]. The unfortunate consequence of this might be that biased clinicians provide less aggressive medical treatment and influence families in ways not appropriate to the situation [37]. Some health care professionals who have no experience with chronic LIS survivors might believe that LIS patients want to die but many studies have shown that patients typically have a wish to live. In 1993, Anderson *et al*. [75] reported that all questioned LIS patients wanted life-sustaining treatment. A previous study by the French ALIS showed that 75% of chronic LIS patients without motor recovery rarely or never had suicidal thoughts. The question: '*would you like to receive antibiotics in*

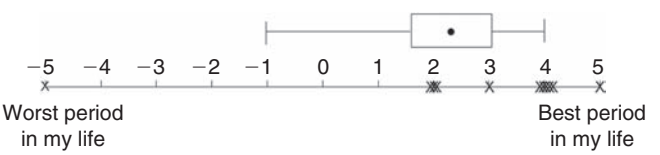


FIGURE 15.7 ACSA [72] showing self-rated quality of life in 11 LIS patients (crosses; mean age 37 ± 6 year; eight males). Box and whiskers represent mean, SD, minimum and maximum of self-rated quality of life in 22 controls (mean age 43 ± 10 year; eight males). Note that on average LIS patients self-rated quality of life is not significantly lower than in controls. *Source*: Adapted from Bruno, Pellas and Laureys [74].

case of pneumonia', 80% answered 'yes' and in reply to the question '*would you like reanimation to be tempted in case of cardiac arrest*', 62% said 'yes'[8]. Similarly, in a recent survey conducted by Bruno *et al*. nearly two-thirds of studied LIS patients ($n = 54$) never had suicidal thoughts (see Figure 15.8) [74]. In line with these findings, Doble *et al*. [37] reported that none of the questioned chronic LIS patients had a 'do not resuscitate' order, more than a half had never considered or discussed euthanasia. These authors also noted that none of the 15 deaths of their study cohort of chronic LIS patients ($n = 29$) could be attributed to euthanasia. Since its creation, the French ALIS has registered over 400 patients with LIS in France. Only five reported deaths were related to the patient's wish to die.

In accordance with the principle of patient autonomy, physicians should respect the right of LIS patients to accept or refuse any treatment. At least two conditions are necessary for full autonomy, patients need to have intact cognitive abilities and they must be able to communicate their thoughts and wishes.

Likewise, in amyotrophic lateral sclerosis, ill-informed patients are regularly advised by physicians to refuse intubation and withhold life-saving interventions [76, 77]. However, ventilator users with neuromuscular disease report meaningful life satisfaction [78]. Bach [79] warns that 'virtually no patients are appropriately counselled about all therapeutic options' and states that advance directives, although appropriate for patients with terminal cancer, are inappropriate for patients with severe motor disability.

Katz *et al*. [36] cite the Hastings Centre Report, 'Who speaks for the patient with LIS?'. With the initial handicap of communicating only through eyeblink who can decide whether the patient is competent to consent or to refuse treatment? [80]. With regard to end-of-life decisions taken in LIS patients, an illustrative case is reported by Fred [81]. His 80-year old mother became locked-in. In concert with the attending physician, without consent of the patient herself, the decision was made to 'have her senses dulled' and provide supportive care only. She died shortly thereafter with a temperature of 109°F (43°C). In the accompanying editorial, Stumpf [82] commented that 'human life is to be preserved as long as there is consciousness and cognitive function in contrast to a vegetative state or neocortical death'.

CONCLUSION

The discussed data stress the need for critical care physicians who are confronted to acute LIS to recognize this infrequent syndrome as early as possible. Health care workers who take care of acute LIS patients need a better understanding of the long-term outcome of LIS. Opposite to the beliefs of many physicians, LIS patients self-report a meaningful quality

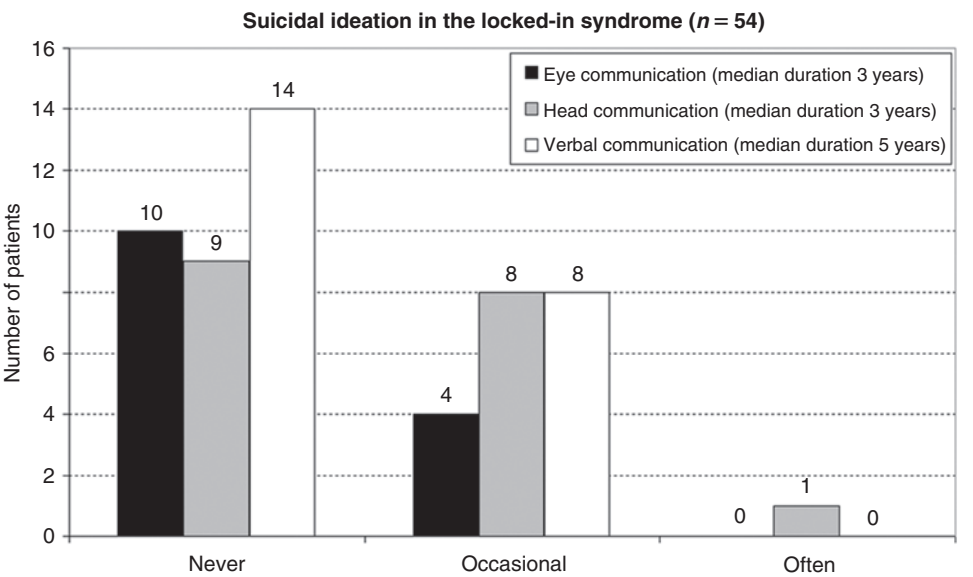


FIGURE 15.8 Frequency of suicide thoughts in 54 patients with chronic LIS (age 22–60 years), 14 communicate with their eyes, 18 have recovered some communication using their head, and 22 have recovered some verbal communication. Note that 33 patients never had suicidal thoughts, 20 had some occasionally and only one patient presented frequent suicide thoughts. *Source*: Adapted from Bruno, Pellas and Laureys [74].

of life and the demand of euthanasia existing but is uncommon. Studies emphasize LIS patients' right to autonomy and demonstrate their ability to exercise it, including taking end-of-life decisions. The strength of medical and communication-technological progress for patients with severe neurological conditions is that it makes them more and more like all the rest of us [83]. Clinicians should realize that quality of life often equates with social rather than physical interaction. It's important to emphasize that only the medically stabilized, informed LIS patient is able to accept or to refuse life-sustaining treatment. LIS patients should not be denied the right to die –and to die – but also, and more importantly, they should not be denied the right to live – and to live with dignity and the best possible care.

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Pharmacological treatments in patients recovering from coma

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Introduction

Disorders of consciousness (DOC) resulting from a severe brain injury include the coma (1), the vegetative state (2) and the minimally conscious state (3). Coma is characterized by a complete absence of arousal and awareness whereas the vegetative/unresponsive syndrome represents an absence of clinical signs of consciousness in spite of a preserved vigilance (opening of the eyes). Patients in a minimally conscious state (MCS) show some signs of consciousness but remain unable to communicate. MCS is now subcategorized in MCS- (non-reflex movements without language comprehension) and MCS+ (command following) (4). If consciousness disorders are currently defined in a clear way, no pharmacological treatment is recognized to improve the level of consciousness of these patients as demonstrated by placebo controlled randomized studies. Evidence based recommendations cannot be provided because there are only a few uncontrolled studies that are methodologically suboptimal (5). Pilot studies and case reports showed that some severely brain-damaged patients could benefit from some pharmacological, rehabilitation or sensory stimulation treatments but, in general, responses to treatment still remain unsatisfactory.

Several pharmacological agents can contribute to the recovery of consciousness in some patients with an altered state of consciousness by targeting various pathways of the central nervous system. Sensory perception is controlled by a complex neural network which includes reticulo-thalamic cholinergic projections, thalamo-cortical and reticulo-cortical glutaminergic projections. Lesions on white matter connections of these networks may perturb consciousness and cognition, and several drugs including dopaminergic agents can act on this network by supporting a recovery of consciousness.

This chapter summarizes the current state of knowledge on potentially useful drugs acting on the recovery of consciousness in severely brain damaged patients and provides indications on the underlying mechanisms possibly explaining the effects of these drugs on the awakening and recovery of consciousness. Exploratory and retrospective studies as well as case reports concerning sporadic cases of spectacular recovery will be discussed regarding drugs as amantadine, levodopa, bromocriptine, apomorphine, methyphenidate, zolpidem, baclofen, sertaline, amitriptyline, desipramine, and lamotrigine (table I).

Potential pharmacological treatments

Amantadine
Amantadine is an old dopaminergic agent initially used in the treatment of Parkinson's disease. For its antiviral properties, amantadine was also employed against influenza. It increases the availability of dopamine in the striatum both at the pre- and post-synaptic level

and facilitates the release of dopamine and delays its recapture, resulting in an increase of synaptic dopamine concentration. At the post-synaptic level, amantadine increases the number of dopaminergic receptors (6). It is also a dose-dependent antagonist of the N-methyl-D-aspartate receptors.
The use of amantadine is correlated with a better outcome among severe traumatic brain injured patients. A retrospective study has showed, for example, that in 74 acute traumatic patients with vegetative state, the group treated with amantadine (n=41) obtained higher scores on the Glasgow Coma Scale (GCS) (7) when discharged from the intensive care unit than the group who did not receive the drug (8). Mortality was also lower in the treatment group (6%) than in the non-treatment group (51%) (8). Another study on 35 patients showed an improvement of behavioral scores (Mini-Mental State Examination (MMSE) (9), Glasgow Outcome Scale (GOS) (10) and Disability Rating Scale (DRS) (11)) during a treatment over six weeks in the acute phase of severe traumatic brain injury (12). Of notice, these two studies took place when the patients were in acute stage and thus presented a bias of spontaneous recovery which may have interfered with the results obtained. A spontaneous recovery may however also occur very tardily in patients with DOC.

Zafonte et al reported a dose dependent response to amantadine in a minimally conscious patient examined 5 months after a cranial trauma. During the treatment, the patient recovered his communication abilities and the score on the Coma/Near Coma (CNC) scale (13) increased. This effect was reversible when stopping the treatment, and during its reintroduction, the patient communicated again (14). Schnakers et al have also shown the benefits of amantadine in a patient who had been in a post-anoxic minimally conscious state for 2 years and who only presented visual pursuit. Following the treatment, he was able to answer commands and the scores of the Coma Recovery Scale – Revised (CRS-R) increased (15, 16). Amantadine has been shown to improve consciousness but also to reduce fatigue, distraction and aggressiveness among 30 patients evaluated between 2 months and 12 years after a traumatic brain injury (17). Finally, in a pediatric population, an improvement has been observed on behavioral scales (CNC, DRS and Western NeuroSensory Stimulation Profile – WSSNP) (18) after taking amantadine and pramipexol (a dopamine antagonist) in 10 children with severe traumatic injury (19). On the other hand, in a group of 123 patients who suffered a severe cranial trauma, the rate of recovery of consciousness was not different between the treatment group and the control group (20).

All the studies quoted up to now used only behavioral scales to objectify the effects of the amantadine treatment. Only one study by Schnakers et al used positron emission tomography (PET) to show an increase in the cerebral metabolic activity in the fronto-parietal network, which is known to be critical for the emergence of consciousness (21), and the sensitivo-motor areas in a minimally conscious patient after the administration of amantadine (16).

Levodopa
As amantadine, levodopa is a dopaminergic agent indicated initially in the treatment of Parkinson's disease. A remarkable recovery has been observed in a 24 years old man with a cranial trauma, diagnosed in a vegetative state for 6 months and who was able to speak a few days after the administration of levodopa (22). Of notice, no standardized validated diagnostic behavioral assessment was done and this as other of the presented reports has been published before the introduction, in 2002, of the criteria of the minimally conscious state and thus the initial diagnosis might have been inaccurate. Five other DOC patients with traumatic lesions also became more responsive after taking levodopa which was initially given to treat extrapyramidal signs (23, 24). Finally, in a last uncontrolled unblinded study, eight patients in

vegetative state recovered signs of consciousness after the administration of progressive amounts of levodopa. All patients could respond to commands within the first two weeks of treatment and seven of them, including two assessed more than 9 months post-injury, were able to interact in a functional way (25).

Bromocriptine

Bromocriptine is another dopamine agonist used primarily to treat Parkinson's disease. This agent, less studied, is mainly an agonist of the post-synaptic dopamine D2 receptors. This treatment was associated with a higher rate of patients recovering from a post-traumatic persistent vegetative state to a minimally conscious state in a retrospective study (26).

Apomorphine

Apomorphine is a non-selective dopaminergic agonist which activates D1 and D2 receptors with a preference for the latter. This therapy is initially indicated to treat Parkinson's disease and erectile impotence but it has also showed positive effects in a few severe brain injured patients. A minimally conscious patient treated with apomorphine 104 days after a brain trauma suddenly recovered consciousness after one day of treatment. He was able to move his legs upon request and to answer yes-no type questions, which was not the case before (27). The patient recovered consciousness and a considerable functional recovery was maintained even after stopping the treatment. Diffusion tensor imaging showed a reduction in thalamo-cortical and cortico-thalamic projections, as expected in these patients. Another uncontrolled case study on eight vegetative and minimally conscious patients with traumatic etiology who were treated continuously with apomorphine showed a recovery of consciousness for all patients except one, with an increase in the CNC and DRS scores (28). These improvements lasted for at least one year, even after stopping the treatment.

Methylphenidate

This agent is initially used for children presenting attention deficit hyperactivity disorders and is also prescribed for narcoleptic patients. This neuro-stimulant increases the release of dopamine and noradrenalin while blocking the reuptake and inhibiting monoamine oxydase (29).

Few studies have been conducted and no conclusive evidence supports the use of a psycho-stimulant to improve the level of consciousness in DOC patients. Only one study suggests that the early use of methylphenidate in intensive care is associated with shorter hospital stays after severe trauma (30). On the other hand, a recent meta-analysis on 22 chronic patients with severe brain damage (17 of traumatic etiology) did not show any clinical improvement on the percentage of responses to command after the administration of methylphenidate (31).

This pharmacological agent could rather have an effect on attention in the acute and sub-acute phases of recovery. Indeed, a subjective improvement of mood, of work-output and vigilance was reported among 14 brain-traumatized patients having attention and memory deficits and being treated with methylphenidate (32). Other studies showed similar positive effects of methylphenidate on attention and memory in patients suffering from moderate brain injury (33).

Finally, 10 children and teenagers in a vegetative state and minimally conscious state were treated with a combination of dopaminergic drugs (amantadine, methylphenidate,

bromocriptine, levodopa, pramipexole) and presented an improvement of responses to structured stimuli in an uncontrolled unblinded prospective study (34).

Zolpidem

Zolpidem is a imidazopyridine which acts like an agonist on sub-type 1 of the inhibiting receptors of the gamma-Aminobutyric acid ($GABA_A$). This agent is initially recommended in the treatment of insomnia and presents sedative, anti-convulsive, anxiolytic and myorelaxant effects.

A number of studies have reported the use of zolpidem as an "awakening" agent among vegetative and minimally conscious patients. This drug produces, occasionally, a clear paradoxical temporary effect on the level of consciousness in patients with severe brain damage. The effect of zolpidem has been described for the first time in 2000 after the fortuitous discovery in an allegedly vegetative patient with cranial trauma for more than 3 years and who started to speak and to communicate with his family twenty minutes after the administration of the medication (35). Clauss et al reported the impressive effects of this drug in 4 vegetative patients who had suffered a traumatic or anoxic cerebral lesion 3 to 5 years before (35, 36). The patients were able to answer questions, to speak and to feed shortly after taking a single dose of zolpidem (10 mg). Improvements were also observed on the GCS scale (increasing from 5-9 to 10-15) and on the Rancho Los Amigos scale (from III to V-VII) (37). The level of consciousness of these patients returned to its initial state four hours after the administration of the drug but an improvement was observed again at the time of re-administration. Similar transitory effects were also reported among patients in minimally conscious state resulting from cerebral anoxia (38, 39, 40).

Only one study investigated the percentage of responders among patients in a vegetative state and in a minimally conscious state (39). Among 15 patients, only one indicated a significant clinical response passing from vegetative to minimally conscious state. The 14 other patients did not show any improvement. The rate of response to zolpidem would thus be close to 7%. Whyte and al suggest that the effect of zolpidem is bimodal rather than gradual since no tendency to improvement of performances was observed among patients who did not respond to the treatment. Several case studies also underlined the absence of improvement among patients suffering from a post-anoxic encephalopathy or a severe cerebral trauma (42, 43, 41).

Several studies were interested in the mechanisms able to explain the effect of zolpidem. Single-photon-emission computed tomography studies showed that zolpidem increases the cerebral metabolism of hypoactive areas following traumatic or anoxic lesions (35, 36, 44). In the same way, using PET in a patient in a minimally conscious state, an improvement of neuropsychological performances was correlated with an increase in cerebral metabolism in the frontal and post-rolandic areas after taking zolpidem. Activations were also observed in anterior cingular and orbito-frontal cortex, areas known to be involved in motivational processes. A mechanism of cell dormancy was introduced to explain the effect of zolpidem: certain nonspecific areas of the brain, adjacent or distant to the initially damaged zones (e.g., the ipsi-lateral, contra-lateral hemisphere or the cerebellum), would be inhibited by the lesion. These inactive parts of the brain would recover their function after taking zolpidem (35, 38, 44, 45), generating a recovery of consciousness. A recent study using magnetoencephalography also showed that zolpidem decreased the number of pathological slow waves associated to dormant cerebral tissue in a patient having undergone a cerebrovascular accident (46).

Zolpidem could thus interact with the limbic loops of the brain by modulating subcortical connections, and more particularly the globus pallidus, which would bring the thalamo-

cortical activity back to normal and would allow a recovery of consciousness (see the mesocircuit model) (47). From a molecular point of view, changes could take place at the levels of glutamate and GABA neuro-transmitters close to the cerebral lesions. The release of glutamate produces an excitotoxicity and an excess of inhibitory GABA neurotransmitters as well as a long-term over-sensitiveness of the $GABA_A$ receptors (35). The inhibitory neurotransmitters, while binding to the receptors of the ionic channels, generate a reduction of metabolism and blood flow in the adjacent cerebral areas thus causing a state of cells dormancy. While binding to $GABA_A$ receptors of dormant cells, zolpidem provokes the inversion of the abnormal state of the neurons and associated metabolic inhibition.

Baclofen

Baclofen is an agonist agent of the $GABA_B$ receptors which acts on the posterior horn of the spinal cord and which is used mainly against spasticity. Spasticity, a frequent symptom following central nervous system lesions, can limit voluntary movements in patients with DOC. Baclofen crossing with difficulty the hematoencephalic barrier, the antispasmodic effect remains modest when it is administered orally. Therefore, a direct and continuous perfusion of baclofen in low doses in the cerebrospinal fluid can be an effective treatment. Intrathecal baclofen therapy can be a useful treatment against severe spasticity among DOC patients improving quality of life by reducing pain related spasms but also by controlling persistent autonomic dysfunctions such as tachycardia, tachypnea, fever and breathing difficulties.

Among vegetative patients who were treated with baclofen, some impressive cases of recovery were reported in uncontrolled case-studies (48, 49, 50). An 8-year-old child, who sustained a severe brain injury following a car accident, received baclofen to treat his spasticity 2 months and half after the accident. Three days after the treatment, the patient started to pronounce words, to answer verbal requests and subsequently showed good recovery. Similarly, an 18-year-old man diagnosed in a “vegetative state” received intrathecal baclofen 1 month and half after his brain trauma. Five days later, he was able to answer verbal requests and was reported to subsequently have recovered motor and cognitive capacities (50). Another case study also showed an impressive recovery in a 11-year-old girl presenting a vegetative state on admission due to diffuse axonal injury following a car accident. After 18 days, she was treated with intrathecal baclofen and was reported to have recovered from spasticity, motor and sensory aphasia (48). Note however that time post-insult was relatively short in these three patients and spontaneous recovery might have occurred as well.

An effect of baclofen was also observed in five allegedly vegetative patients treated for spasticity in the chronic stage (at least 19 months after the injury). Two weeks after, all except one patient presented a clinical improvement which remained stable until the end of the 6 months follow-up. Improvements went from a high increase in vigilance to a recovery of consciousness, as revealed by the changes in the CRS-R scores (51). Finally, in a last case study, after the introduction of intrathecal baclofen, a 44-year-old man recovered consciousness 19 months after a non-traumatic brain injury (i.e., subarachnoid hemorrhage due to a ruptured aneurysm). He however remains dependent on others for his activities of daily living (49).

Several assumptions have been made to explain the effects of baclofen on recovery of consciousness. Some authors suggest a modulation of motor impulses of the spinal cord on the possible cortical reactivation (51). Baclofen would improve nervous conduction in the

demyelinized axons and could possibly accelerate the restoration of diffuse axonal injury (52). A modulation of the sleep-wake cycle has also been considered as a mechanism responsible for the effect of baclofen (51). But all these explanations at present remain hypothetical.

Serotonin-reuptake inhibitors
Sertalin is an antidepressant of the selective serotonin reuptake inhibitor class. Acute brain lesions have been reported to increase cerebral serotonin but in the chronic phase a down regulation of the serotonin system is thought to occur. In a prospective placebo-controlled randomized study, sertalin treatment did not improve the level of consciousness among 11 severely brain injured patients (53). On the other hand, amitriptylin and desipramin treatment (tricyclic antidepressants also blocking the recapture of serotonin) was reported in an uncontrolled unblinded study to improve recovery in three patients with severe traumatic brain injury (54). Two of these patients presented a deterioration when the drug was stopped but an improvement was again observed at the time of reintroduction of the treatment. The third patient started to talk after being mute for more than one year. The possible mechanisms of action in this context remain largely unexplained.

Lamotrigin
Lamotrigin is an anti-epileptic agent used in the treatment of epilepsy and bipolar disorders. By inhibiting the voltage-dependent sodium channels, it stabilizes the neuronal membrane and inhibits glutamate release, an excitatory neurotransmitter. The effects on the sodium ion channels contribute to the anti-epileptic effects and the anti-glutamatergic agents act more on the psychotropic effects with a possible neuroprotective action. Functional improvement of DOC patients has been observed after administration of lamotrigin, showing recovery of consciousness and cognition and an earlier discharge from hospital (55). This uncontrolled unblinded study concluded a possible effect on functional recovery and particularly in patients who had already emerged from the minimally conscious state.

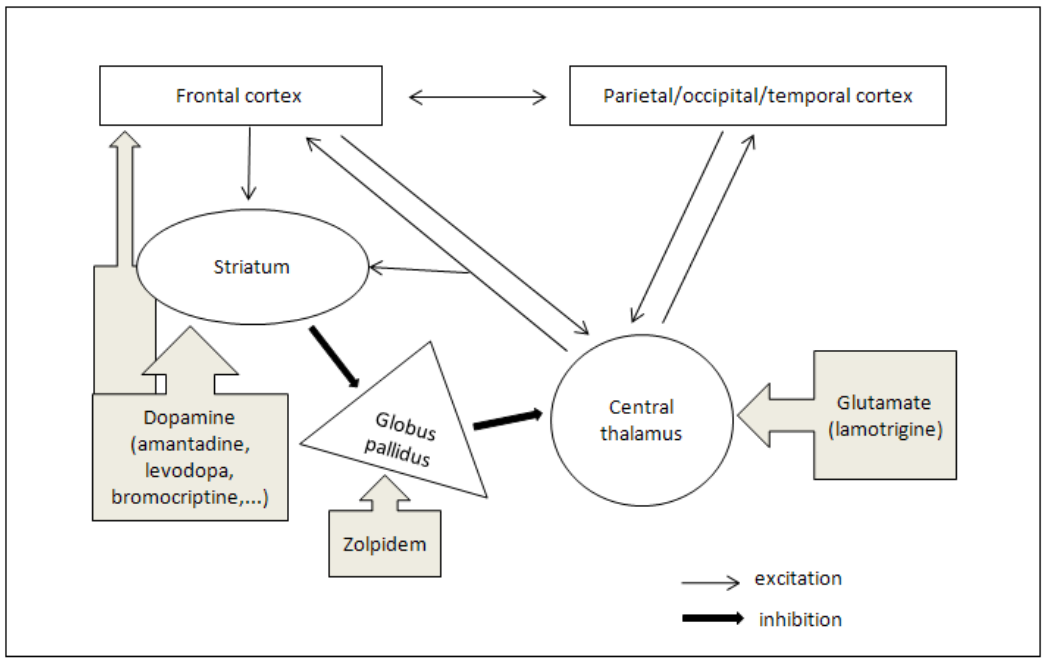
Mechanisms aiming to explain the possible positive effects of pharmacological treatments

Each drug affects one or more neuronal pathways. Amantadine, levodopa, bromocritpine, methylphenidate and apomorphine act mainly on the dopaminergic system whereas zolpidem and baclofene affect preferentially the gabaergic system (albeit at different locations in the nervous system) while sertraline, amitriptyline and desipramine interfere rather in serotoninergic processes. The subjacent neurological mechanisms to the positive effects of these drugs are currently not well understood. As we have seen, amantadine and zolpidem would increase the metabolism of hypoactive cerebral regions (16, 56). Zolpidem would play a main role in the gabaergic system of the limbic loops in the brain (57) whereas Baclofen would act more on the spinal cord and would support the regeneration of motor neurons (51).

The model of the mesocircuit has been proposed recently to explain the various pharmacological effects on recovery of consciousness (47, 57) (fig. 1). Central thalamic nuclei (CTN) seem particularly important in the emergence of consciousness. They receive ascending projections coming from the brainstem encompassing the arousal systems that control the activity of many cortical and thalamic neurons during the sleep-wake cycle. CTN are strongly nerved by cholinergic, serotoninergic, noradrenergic afferents of the arousal systems in the brainstem. These same neurons of the CTN are also innervated by downward projections coming from the areas of the frontoparietal cortex. Collectively, these ascending

and descending pathways seem to modulate the level of consciousness (57). The frontoparietal cortex (and its subcortical modulation via striatum, globus pallidus and thalamus) is also prevalent for the emergence of consciousness. Thalamo-cortical projections coming from the CTN activate in normal conditions the neurons of the cortex and striatum. Lesions at this level result in a reduction of cerebral metabolism. Neurons of the striatum inhibit the internal globus pallidus but require a strong basic synaptic activity and elevated levels of dopaminergic innervations in order to maintain their state in activity. Without projections of the striatum to the globus pallidus (e.g. by a lack of dopaminergic innervations) the globus pallidus itself will inhibit the CTN which in turn will inhibit the cortical structures, and this sequence could thus generate consciousness disorders. Disturbances in this mesocircuit influences the total dynamics of the dominating cortico-thalamic and frontoparietal systems (58). Dopaminergic drugs could therefore facilitate projections of the striatum on the globus pallidus which would modulate the frontoparietal cortical neurons and would restore the cortico-subcortical loops. Zolpidem is thought to act directly on the globus pallidus and would make it possible to inhibit it (as it is usually the case due to the action of the striatum) which would also restore the activity of the CTN, whereas the glutamatergic agents (e.g., lamotrigine) would intervene directly on the CTN (fig. 1).

Fig. 1 - Model of the mesocircuit that aims to explain the mechanisms of pharmacologically induced recovery of consciousness.



Adapted from Schiff and al (2010), Trends in Neuroscience

Table I – Pharmacological treatment studies aiming to improve the level of consciousness in patients with severe brain damage with chronic disorders of consciousness

Pharmacological agent	Study (first author, year)	N/ Etiol.	Diagnostic	Interv lesion-treatment	Treatment	Effect	Results	Type of study	Ref
Dopaminergic agent									
Amantadine	Schnakers (2008)	1anox	MCS	2 years	200 mg/d for 6 w	+	↑ CRS-R score, response to command, automatic motor behavior	prospective, ABAB paradigm	(16)
	Patrick (2006)	10TBI	VS/MCS	> 1 month	50 mg/d for 3 w, 100 mg/d for 1w, 50 mg/d for 2 w	+	↑ CNC, WNSSP, DRS scores	prospective, double blind randomized	(19)
	Hughes (2005)	123TBI	severe lesion	± 6 weeks	2x100 mg for 1 w, 200 mg 2x/d for 2 w	/	no improvement	retrospective	(20)
	Saniova (2004)	41TBI	VS	< 3 months	200 mg 2x/d for 3 d	+	↑ GCS score, ↓ mortality	retrospective	(8)
	Meythaler (2002)	35TBI	MCS	4 days to 6 weeks	200 mg/d for 6 weeks	+	↑ MMSE, GOS, DRS scores	prospective, placebo controlleddouble blind randomized	(12)
	Zafonte (1998)	1TBI	MCS	5 months	100 mg/d, ↑100 mg/5d with maximum 400 mg/d. After 35 d, diminution 100 mg/5d, when 100 mg/d, ↑ again	+	emergence of MCS, ↑ CNC score, active participation	case study, ABAB paradigm	(14)
	Gualtieri (1989)	30TBI	moderate to severe lesion	2 to 144 months	50-100 mg/d, ↑ 50-100 mg/w during 6 w up to 1 year. If no response, stop treatment after 6w	+	↑ awakening, ↓ tiredness, ↓ distractedness and ↓ aggressiveness	case study	(17)
Levodopa	Matsuda (2005)	5TBI	VS/MCS	3 to 22 months	up to 450 mg/d	+	emergence from VS and MCS, response to command, verbal and written production, functional communication	case study	(24)
	Krimchansky (2004)	8TBI	VS	1 to 7 months	5/250 mg (carbidopa), 25% of a tablet 3x/d, ↑ of a quarter of tablet every w. Maximum 3 tablets/d	+	response to command within 2 w, functional communication within one month, 1 patient remains MCS	prospective	(25)
	Matsuda (2003)	3TBI	VS	3 to 12 months	100/25 mg (carbidopa) 2 to 3x/d	+	response to command, visual pursuit, “yes-no” communication	case study	(23)
	Haig (1990)	1TBI	VS	6 months	100/10 mg (carbidopa) 2x/d	+	response to command, verbal communication	case study	(22)
Bromocriptine	Passler	5TBI	VS	33 to 50	1.25 mg 2x/d then 2,5 mg 2x/w for	+	rate of transition VS-MCS larger than	case study	(26)

	(2001)			days	2 to 6 months		normal, ↑ DRS and CRS-R scores, functional communication		
Apomorphine	Fridman (2010)	8TBI	VS/MCS	1 to 4 months	± 5 mgml-1, begins with ratio of 2 mgh-1 for 12h/d up to 8 mgh-1for 12 to16 h/d for 6 months	+	↑ awakening, ↑ CNC and DRS scores, response to command, functional communication for all except one patient	case study	(28)
	Fridman (2009)	1TBI	MCS	104 days	± 5 mgml-1, begins with ratio of 2 mgh-1 for 12h/d up to 8 mgh-1 for 12 to 16 h/d for 6 months	+	response to command, "yes-no" communication, ↑ CNC, DRS, GOS scores	prospective case study	(27)
Methylphenidate	Martin (2007)	22 (17 TBI)	VS/MCS	3 months to 8 years	between 7.5 and 25 mg 2x/d	/	no difference in the rate and accuracy of responses to command	retrospective meta-analysis	(31)
	Moein (2006)	40TBI	severe lesion	<3weeks	between 0,3 and 20 mg/kg/dose 2x/d during hospitalization	+	↓ duration of hospital stay (23%)	prospective, double blind placebo-controlled randomized	(30)
Drug combinations	Patrick (2003)	10 (7 TBI)	VS/MCS	22 days to 4 months	amantadine 100-200/d, bromocriptine 0,125 to 400 mg/d methylphenidate 10 to 80 mg/d levodopa 25/100 mg/d or pramipexole 0,125-0,5 mg/d for 7 to 132 d	+	↑ WNSSP scores, ↑ responses to structured stimuli, ↑ of the recuperation ratio	case study, ABA paradigm	(34)
GABAergic agent									
Zolpidem	Whyte (2009)	15 (8TBI)	VS/MCS	3 months to 23 years	10 mg	+ and /	only 1 responder to treatment (VS to MSC), ↑ score CRS-R, visual pursuit, response to command	multi-centric, double blind randomized	(41)
	Cohen (2008)	1anox	MCS	8 months	5 mg/d then 10 mg/d for 3 w then 20 mg/d	+	↑arousal, ↑ interactions, ↑ verbal and social responses	case study	(39)
	Shames (2008)	1anox	MCS	18 months	10 mg	+	↑ arousal, ↑ RLAS score, ↑ verbal communication, reading, counting, verbal production, auto-alimentation	case study	(40)
	Singh (2008)	1TBI	MCS	4 years	10 mg/d for 1 week	/	no effect on tests with instructions which ↑ in complexity	single blind case study	(43)
	Lo (2008)	2anox	VS	± 1 month	10 mg for 2 days, repeated once 2 days later	/	no arousal improvement, no recovering of consciousness, no ↑ GCS score	double-blind case study	(42)
	Brefel-Courbon (2007)	1anox	MCS	2 years	20 mg/j for 1 w	+	↑ arousal, ↑ motor and neuropsychological performance (functional communication, eating, walking, reading and repeating words)	prospective double blind, placebo-controlled	(38)

								randomized	
	Clauss (2006)	2TBI and 1 anox	VS	3 to 5 years	10 mg/d for 3, 5 et 6 years	+	↑ arousal, ↑ GCS and RLAS scores	case study	(36)
	Clauss (2000)	1TBI	semi-comatose	3 years	10 mg	+	verbal response after 15 minutes, talking, answering simple questions, spontaneous interaction, counting, writing	case study	(35)
Baclofen	Sara (2009)	5(2TBI)	VS	6 to 10 months	100 mg/d continuously, up to 200 mg/d	+	↑ arousal, ↑ CRS-R score, response to command	case study	(51)
	Sara (2007)	1non-TBI	VS	19 months	100 mg/d continuously, up to 200 mg/d	+	VS to MCS, verbal communication, "yes-non" communication, eating, emotional response	case study	(47)
	Taira (2007)	2TBI	VS	1.5 to 2.5 months	50 mg/d for 3 d then 75 mg/d for l0 d and 100 mg/d for l0d then 50 mg/d for 5d then 100 mg/d for 23 d	+	↑ arousal, response to command	case study	(48)
	Kawecki (2007)	1TBI	VS	18 days	100 mg/d	+	spasticity, motor and sensory aphasia improvement	case study	(46)
Serotoninergic agent									
Sertaline	Meythaler (2001)	11TBI	severe lesion	<2 weeks	100 mg/d for 2 w	/	no improvement	prospective, placebo-controlled randomized blinded	(51)
Amitriptyline and desipramine	Reinhard (1996)	3TBI	severe lesion	2 to 19 months	50 to 75 mg/d	+	↑ arousal and initiation, response to command, “yes-no” communication, verbal communication	case study	(54)
Anti-convulsive agent									
Lamotrigine	Showalter (2000)	13 (6TBI)	severe lesion	20 days to 10 months	150 to 400 mg	+	↑ of consciousness and cognition, discharge from hospital sooner than expected	case study	(55)

Abbreviations: N= number of patients, etiol= etiology, interv= interval, TBI= traumatic brain injury, anox= anoxia, VS= vegetative state, MCS= minimally conscious state, d= day, w = week, mg= milligram, ↑ =improvement, ↓= decrease, + = positive, / = no effect, MMSE=Mini Mental State Examination, GOS= Glasgow Outcome Scale, DRS= Disability Rating Scale , CRS-R=Coma Recovery Scale-Revised , RLAS= Rancho Los Amigos Scale, GCS=Glasgow Coma Scale , CNC= Coma Near Coma Scale, WNSSP=Western Neuro Sensory Program Stimulation.

Conclusion

No strong evidence currently supports or disproves the specific use of a pharmacological agent in order to improve consciousness in DOC patients of a well-defined etiology and duration. As discussed, a number of small and uncontrolled case or cohort studies have reported a positive clinical response. Indeed, transitory or permanent improvements were observed among some allegedly "vegetative" or minimally conscious patients of various etiologies (cranial traumatism, cerebrovascular accident, anoxia, etc). Reported effects were variable ranging from increases in wakefulness, partial recovery of consciousness, motor, verbal, or communication functions to "full" recovery of cognitive functioning (albeit ill described).

Some of the reviewed treatments seem to benefit patients with severe disorders of consciousness (e.g., amantadine, zolpidem, baclofen) whereas others (e.g., methylphenidate, lamotrigine) seem to possibly be more beneficial for brain-damaged but conscious patients improving cognitive disorders of attention deficits (59). The effects were observed in the short and long-term, and this, generated by a single dose (e.g., zolpidem) or by a continuous treatment (e.g., amantadine, baclofen, levodopa).

To date, the absence of double-blind placebo-controlled randomized multi-centric studies do not permit to propose any evidence-based therapeutic guidelines for a specific diagnostic entity of DOC (vegetative versus minimally conscious state), taking into account etiology and duration of the brain damage. Indeed, the reported data come from case or cohort reports, presenting methodological limitations not permitting to disentangle the drug effect from the natural evolution of the disease. Studies including a broader number of patients are especially influenced by the extreme heterogeneity of DOC, such as the site of neuropathological lesions, time elapsed between injury and the introduction of the treatment, confounding drugs received and medical comorbidities. Moreover, it is difficult to compare between studies since they lack homogeneity in methodology and differ in the duration of treatment, administered doses, and patients' demographics and clinical status (table I). Employed measurement tools and behavioral scales are also very different according to the studies (e.g., CRS-R, DRS, GCS, CNC, WSSNP) and a standardization of bedside assessment seems necessary. The most adapted scale in this context is the Coma Recovery Scale-Revised which has been specifically developed to distinguish between vegetative and minimally conscious patients (60). Obviously, placebo-controlled, double-blind randomized multicentric studies are necessary before drawing any conclusion on the effectiveness of therapeutic treatments in these challenging patients.

Even if several hypotheses have been proposed, such as the mesocircuit model, there is still a need to better understand the mechanisms and involved neurotransmitters systems underlying residual neural plasticity and recovery from severe brain damage. It would also be an improvement for the field to develop biomarkers of recovery of consciousness using neuroimagery or electrophysiology and to better define therapeutic responders (e.g., genetic markers). It could also be useful (albeit methodologically more complicated) to test the efficacy of a combination of different pharmatherapeutic agents and/or combinations with non-pharmacological rehabilitation interventions and this by refining the timing of coercive interventions (therapy based on amount and intensity). The non-pharmacological interventions such as physical and cognitive rehabilitation as well as the sensory stimulation programs are complementary and essential in the therapy planning of DOC patients. Finally, deep brain stimulation is currently being investigated as a therapeutic option in some selected patients with post-traumatic minimally conscious state but still remains in the research field and should be more investigated before implementing it in the clinical routine (61).

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Maslach Burn Out Inventory

Age :_____ Sexe : _____ Profession : _____ Centre : _____ Nombre d'années passées en contact avec les patients végétatifs (VS) et en état de conscience minimale (MCS) :_____ Nombre d'heures par semaine consacrées aux patients VS et MCS : _____

	Jamais	Quelques fois par an	Une fois par mois	Quelques fois par mois	Une fois par semaine	Quelques fois par semaine	Chaque jour
1-Je me sens émotionnellement vidé(e) par mon travail							
2-Je me sens à bout à la fin de ma journée de travail							
3-Je me sens fatigué(e) lorsque je me lève le matin et que j'ai à affronter une autre journée de travail							
4-Je peux comprendre facilement ce que mes malades ressentent							
5-Je sens que je m'occupe de certains malades de façon impersonnelle comme s'ils étaient des objets							
6-Travailler avec des gens tout au long de la journée me demande beaucoup d'effort							
7-Je m'occupe très efficacement des problèmes de mes malades							
8-Je sens que je craque à cause de mon travail							
9-J'ai l'impression, à travers mon travail, d'avoir une influence positive sur les gens							
10-Je suis devenu(e) plus insensible aux gens depuis que j'ai ce travail							
11-Je crains que ce travail ne m'endurcisse émotionnellement							
12-Je me sens plein(e) d'énergie							
13-Je me sens frustré(e) par mon travail							
14-Je sens que je travaille « trop dur » dans mon travail							
15-Je ne me soucie pas vraiment de ce qui arrive à certains de mes malades							
16-Travailler en contact direct avec les gens me stresse trop							
17-J'arrive facilement à créer une atmosphère détendue avec mes malades							
18-Je me sens ragaillardi(e) lorsque dans mon travail j'ai été proche de mes malades							
19-J'ai accompli beaucoup de choses qui en valent la peine dans ce travail							
20-Je me sens au bout du rouleau							
21-Dans mon travail, je traite les problèmes émotionnels très calmement							
22-J'ai l'impression que mes patients me rendent responsable de certains de leurs problèmes							

Questionnaire sur les besoins de la famille d'un patient sévèrement cérébrolésé

Date du jour: ……..... **Votre âge: ..... Sexe: ..... Profession**: ……..

Votre lien de parenté :…….

Age de votre proche: ..... Date de la lésion cérébrale: .....

Province :……...

☐ Centre de rééducation ☐ Maison de soins et de nursing ☐ Domicile

Diagnostic:

☐ Coma (pas d'ouverture des yeux)
☐ Etat végétatif (ouverture des yeux, mouvements réflexes uniquement)
☐ Etat de conscience minimale (plus que des mouvements réflexes – par ex : poursuite visuelle ou réponse à la commande mais sans communication fonctionnelle)
☐ Sortie de l'état de conscience minimale (communication fonctionnelle)
☐ Syndrome locked-in

Gastrostomie actuellement : ☐oui ☐non

Trachéotomie actuellement : ☐oui ☐non

❖ Quels sont les problèmes que vous avez rencontrés lors de la prise en charge de votre proche (depuis l'accident à maintenant)?

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❖ Quelles sont les solutions éventuelles que vous avez trouvées ou que vous suggérez pour la prise en charge de votre proche?

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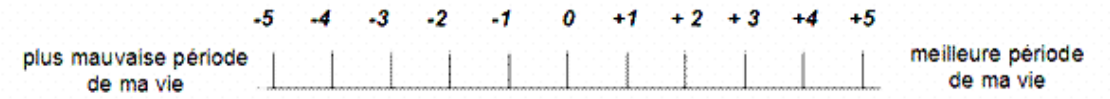
Entourer dans la partie A et dans la partie B la réponse qui vous correspond le plus (**1=pas du tout important ; 2=peu important ; 3=assez important ; 4=très important**). Merci de répondre à toutes les questions.

J'ai besoin…	**Partie A** *A quel point ce besoin est important à mes yeux ?*				**Partie B** *Ce besoin est-il satisfait ?*		
1.de voir que le personnel soignant respecte les besoins et les souhaits du patient	1	2	3	4	Oui	Partiellement	Non
2.d'être, quotidiennement, mis au courant de ce qui a été fait auprès du patient	1	2	3	4	Oui	Partiellement	Non
3.de donner , quotidiennement, mon opinion au personnel soignant	1	2	3	4	Oui	Partiellement	Non
4.d'être mis courant du moindre changement dans l'état médical du patient	1	2	3	4	Oui	Partiellement	Non
5.d'être assuré que les meilleurs soins sont fournis au patient	1	2	3	4	Oui	Partiellement	Non
6.d'avoir des explications de professionnels formulées de manière à ce que je puisse comprendre	1	2	3	4	Oui	Partiellement	Non
7.d'avoir des réponses honnêtes à mes questions	1	2	3	4	Oui	Partiellement	Non
8.de voir que mes opinions sont pris en compte dans la prise en charge du patient	1	2	3	4	Oui	Partiellement	Non
9.d'avoir un professionnel vers qui me tourner quand le patient a besoin d'aide	1	2	3	4	Oui	Partiellement	Non
10.d'avoir des informations complètes sur les soins médicaux en cas de lésions cérébrales sévères (médications, chirurgie, etc.)	1	2	3	4	Oui	Partiellement	Non
11.d'avoir des informations complètes sur les problèmes physiques du patient (vision, marche, migraines, etc.)	1	2	3	4	Oui	Partiellement	Non
12.d'avoir des informations complètes sur les problèmes cognitifs du patient (confusion, mémoire ou communication)	1	2	3	4	Oui	Partiellement	Non
13.d'avoir des informations complètes sur les traitements	1	2	3	4	Oui	Partiellement	Non
14.de savoir combien de temps chacun des problèmes du patient est censé durer	1	2	3	4	Oui	Partiellement	Non
15.de savoir comment réagir quand le patient est étrange ou en colère	1	2	3	4	Oui	Partiellement	Non
16.d'avoir des informations quant aux progrès du patient	1	2	3	4	Oui	Partiellement	Non
17.de savoir à quel point laisser le patient faire par lui-même	1	2	3	4	Oui	Partiellement	Non
18.d'avoir assez de ressources pour le patient (programme de revalidation, prise en charge médicale, etc.)	1	2	3	4	Oui	Partiellement	Non
19.d'avoir assez de ressources pour moi-même ou ma famille (assistance financière et juridique, soins à domicile, etc.)	1	2	3	4	Oui	Partiellement	Non
20.d'avoir une aide dans la maintenance de mon domicile (nettoyage, repas, courses, etc.)	1	2	3	4	Oui	Partiellement	Non
21.d'avoir de l'aide d'autres membres de ma famille dans la prise en charge du patient	1	2	3	4	Oui	Partiellement	Non
22.de pouvoir dormir ou me reposer suffisamment	1	2	3	4	Oui	Partiellement	Non
23.d'avoir un break afin de m'écarter de mes problèmes et responsabilités	1	2	3	4	Oui	Partiellement	Non
24.de passer du temps avec mes amis	1	2	3	4	Oui	Partiellement	Non
25.de faire attention à mes propres besoins, à mon travail, à mes propres intérêts	1	2	3	4	Oui	Partiellement	Non
26.de savoir que le patient comprend combien c'est difficile pour moi	1	2	3	4	Oui	Partiellement	Non
27.de savoir que mon partenaire ou mes amis comprennent combien c'est difficile pour moi	1	2	3	4	Oui	Partiellement	Non
28.de savoir que les autres membres de la famille comprennent les problèmes du patient	1	2	3	4	Oui	Partiellement	Non
29.de savoir que les amis du patient comprennent les problèmes du patient	1	2	3	4	Oui	Partiellement	Non
30.de savoir que le patron, les collègues ou l'enseignant du patient comprennent les problèmes de celui-ci	1	2	3	4	Oui	Partiellement	Non
31.de parler de ce que je vis avec quelqu'un qui est passé par les mêmes expériences	1	2	3	4	Oui	Partiellement	Non
32.de parler de ce que je vis avec mes amis ou ma famille	1	2	3	4	Oui	Partiellement	Non
33.d'être assuré qu'il est normale d'éprouver des sentiments négatifs envers le patient	1	2	3	4	Oui	Partiellement	Non
34.de recevoir de l'aide pour apaiser mes doutes et mes peurs concernant le futur	1	2	3	4	Oui	Partiellement	Non
35. de recevoir de l'aide pour continuer à espérer concernant le futur du patient	1	2	3	4	Oui	Partiellement	Non
36. de recevoir de l'aide pour me préparer au pire	1	2	3	4	Oui	Partiellement	Non

37.d'être encouragé à demander de l'aide autour de moi	1	2	3	4	Oui	Partiellement	Non
38. de trouver un médecin traitant connaissant les problèmes liés à la prise en charge des patients en état de conscience altérée.	1	2	3	4	Oui	Partiellement	Non
39. de recevoir des informations sur l'aménagement éventuel de mon domicile, sur l'équipement nécessaire, et sur les aides matérielles existantes.	1	2	3	4	Oui	Partiellement	Non
40. d'avoir la possibilité d'engager une aide extérieure ou de trouver une institution adaptée pour la prise en charge et/ou la surveillance du patient si j'ai des problème de santé ou si je suis absent(e).	1	2	3	4	Oui	Partiellement	Non

Etude de la qualité de vie

- Pensez au moment le moins heureux de votre vie (sur l'échelle, ce moment vaut -5) et ensuite au moment le plus heureux de votre vie (ce moment vaut +5 sur l'échelle). Puis indiquez sur cette échelle **par une seule croix** votre degré de bien-être durant ces deux dernières semaines.



- Je ☐ ne suis pas anxieux(se)
  ☐ suis modérément anxieux(se)
  ☐ suis extrêmement anxieux(se)

- Etes-vous déprimé ? ☐Souvent
  ☐Occasionnellement
  ☐Jamais

- Si l'euthanasie était légalement possible pour votre proche :
  ☐ Vous l'auriez envisagé à un moment mais plus maintenant
  ☐ Vous ne l'auriez jamais envisagé
  ☐ Vous la souhaiteriez maintenant

- Actuellement, vous opteriez pour quel code à l'égard de votre proche :
  ☐ Code 0: pas de limites à la thérapie
  ☐ Code 1: ne pas réanimer
  ☐ Code 2: ne plus ajouter une thérapie ou ne plus étendre la thérapie en cours
  ☐ Code 3: arrêt progressif de la thérapie

- Remarques éventuelles :

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UN GRAND MERCI POUR VOTRE COLLABORATION!

