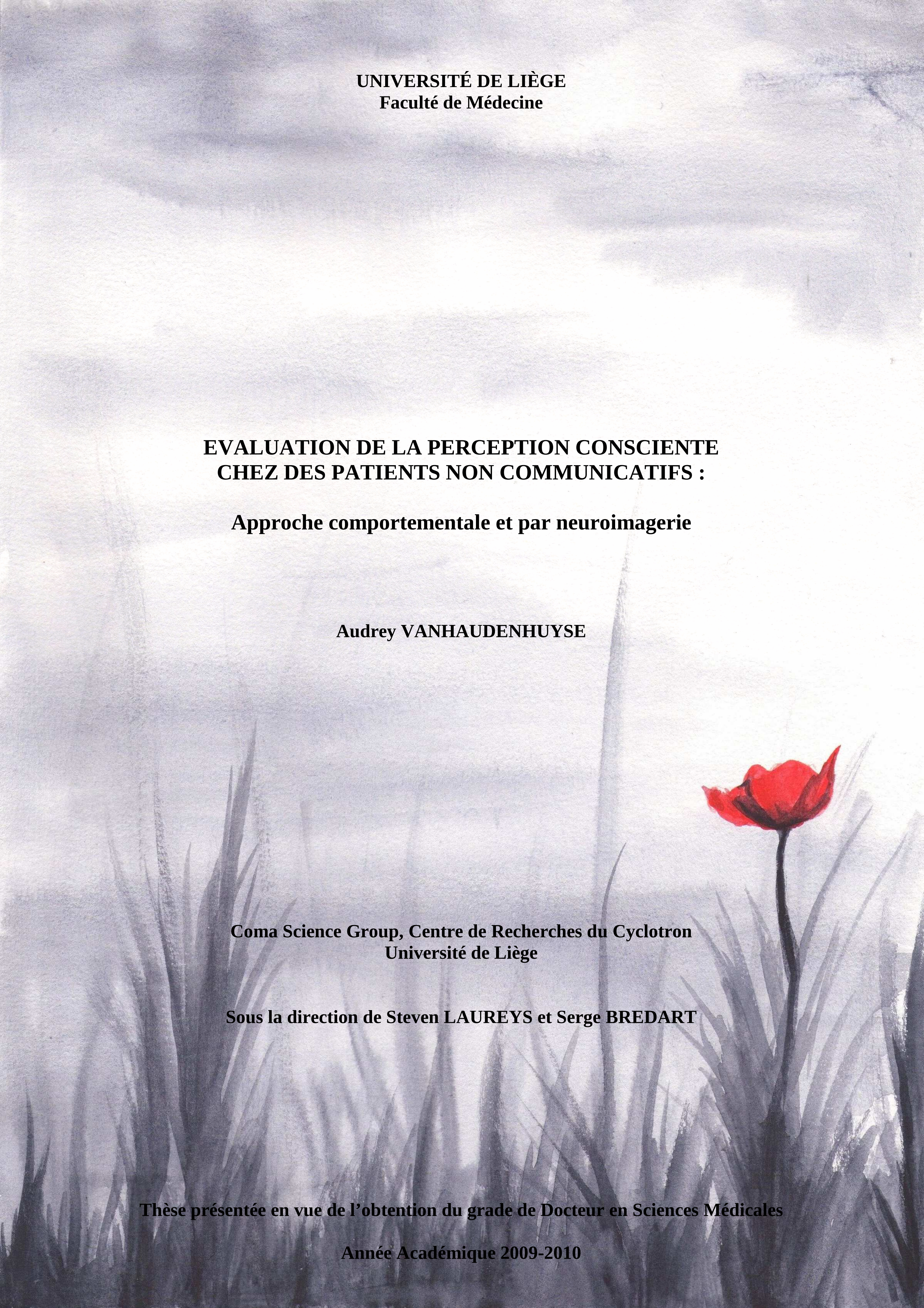


UNIVERSITÉ DE LIÈGE
Faculté de Médecine

EVALUATION DE LA PERCEPTION CONSCIENTE CHEZ DES PATIENTS NON COMMUNICATIFS :

Approche comportementale et par neuroimagerie

Audrey VANHAUDENHUYSE

Coma Science Group, Centre de Recherches du Cyclotron
Université de Liège

Sous la direction de Steven LAUREYS et Serge BREDART

Thèse présentée en vue de l'obtention du grade de Docteur en Sciences Médicales

Année Académique 2009-2010

Première et quatrième de couverture
Alinoë Vanhaudenhuyse

UNIVERSITÉ DE LIÈGE
Faculté de Médecine

EVALUATION DE LA PERCEPTION CONSCIENTE CHEZ DES PATIENTS NON COMMUNICATIFS :

Approche comportementale et par neuroimagerie

Audrey VANHAUDENHUYSE

Coma Science Group
Centre de Recherches du Cyclotron
Université de Liège

Sous la direction de Steven LAUREYS et Serge BREDART

Thèse présentée en vue de l'obtention du grade de Docteur en Sciences Médicales

Année Académique 2009-2010

TABLE DES MATIERES

I. Vegetative state. Vanhaudenhuyse A., Boly M., Laureys S. *Scholarpedia* 2009: 4, 4163

II. Detecting consciousness in minimally conscious patients. Vanhaudenhuyse A., Schnakers C., Boly M., Perrin F., Bredart S., Laureys S. *Reanimation* 2007: 16, 527-532

III. Locked-in syndrome and disorders of consciousness: how to detect consciousness? Vanhaudenhuyse A., Bruno MA., Schnakers C., Boly M., Boveroux P., Moonen G., Perrin F., Pellas F., Pantke KH., Laureys S. In: *Pellas F., Kiefe, C., Weiss J., Pélissier J. (Eds.), Eveil de coma et états limites. Etats végétatifs, états pauci-relationnels et locked-in syndrome.* Masson, Issy-les-Moulineaux, 2007: pp. 109-116

IV. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. Schnakers C., Vanhaudenhuyse A., Giacino J., Ventura M., Boly M., Majerus S., Moonen G., Laureys S. *BMC Neurology* 2009: 9, 35

V. The Sensory Modality Assessment and Rehabilitation Technique (SMART): a behavioral assessment scale for disorders of consciousness. Chatelle C., Schnakers C., Bruno MA., Gosseries O., Laureys S., Vanhaudenhuyse A. *Revue Neurologique* 2010: in press

VI. Assessment of visual pursuit in post-comatose states: use a mirror. Vanhaudenhuyse A., Schnakers C., Bredart S., Laureys S. *Journal of Neurology Neurosurgery and Psychiatry* 2008: 79, 223

VII. Blink to visual threat does not herald consciousness in the vegetative state. Vanhaudenhuyse A., Giacino J., Schnakers C., Kalmar K., Smart C., Bruno MA., Gosseries O., Moonen G., Laureys S. *Neurology* 2008: 71(17):1374-5

VIII. Is there anybody in there? Detecting awareness in disorders of consciousness. Demertzi A., Vanhaudenhuyse A., Bruno MA., Schnakers C., Boly M., Boveroux P., Maquet P., Moonen G., Laureys S. *Expert Review of Neurotherapeutics* 2008: 8, 1719-30

IX. Cognitive event-related potentials in comatose and post-comatose states. Vanhaudenhuyse A., Laureys S., Perrin F. *Neurocritical Care* 2008: 8, 262-270

X. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Vanhaudenhuyse A., Noirhomme Q., Tshibanda L., Bruno MA., Boveroux P., Schnakers C., Soddu A., Perlbarg V., Ledoux D., Brichant JF., Moonen G., Maquet P., Greicius MD., Laureys S., Boly M. *Brain* 2010: 133, 161-171

XI. Two distinct neuronal networks mediate the awareness of environment and of self. Vanhaudenhuyse A. & Demertzi A., Schabus M., Noirhomme Q., Bredart S., Boly M., Phillips C., Soddu A., Luxen A., Moonen G., Laureys S. *Journal of Cognitive Neurosciences* 2010: in press

XII. Willful Modulation of Brain Activity in Disorders of Consciousness. Monti M. & Vanhaudenhuyse A., Coleman M., Boly M., Pickard J., Tshibanda L., Owen A., Laureys S. *The New England Journal of Medicine* 2010: 362(7):579-589

XIII. Disorders of consciousness: moving from passive to resting state and active paradigms. Bruno MA., Soddu A., Demertzi A., Laureys S., Gosseries O., Schnakers C., Boly M., Noirhomme, Q., Thonnard M., Chatelle C., Vanhaudenhuyse A. *Cognitive Neurosciences* 2010: in press

XIV. The challenge of disentangling reportability and phenomenal consciousness in post-comatose states. Vanhaudenhuyse A., Bruno MA., Bredart S., Plenevaux A., Laureys S. *Behavioral Brain Science* 2007: 30, 529-530

XV. Neuroimaging after coma. Tshibanda L. & Vanhaudenhuyse A., Boly M., Soddu A., Bruno MA., Moonen G., Laureys S., Noirhomme Q. *Neuroradiology* 2009: 52(1), 15-24

XVI. Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls. Tshibanda L. & Vanhaudenhuyse A., Galanaud D., Boly M., Laureys S., Puybasset L. *Progress in Brain Research* 2009: 177, 215-229

AUTRES PUBLICATIONS SCIENTIFIQUES

I. Pain and non-pain processing during hypnosis: a thulium-YAG event-related fMRI study. Vanhaudenhuyse A., Boly M., Balteau E., Schnakers C., Moonen G., Luxen A., Lamy M., Degueldre C., Brichant JF., Maquet P., Laureys S., Faymonville, ME. *Neuroimage* 2009: 47, 1047-1054

II. Towards a Neuro-scientific Explanation of Near-death Experiences? Vanhaudenhuyse A., Thonnard M., Laureys S. *Yearbook of Intensive Care and Emergency Medicine*. Ed. Springer Berlin Heidelberg 2009: 961-968

III. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Boly M., Phillips C., Tshibanda L., Vanhaudenhuyse A., Schabus M., Dang-Vu TT., Moonen G., Hustinx R., Maquet P., Laureys S. *Annals of the New York Academy of Sciences* 2008: 1129, 119-29

IV. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Boly M., Tshibanda L., Vanhaudenhuyse A., Noirhomme Q., Schnakers C., Ledoux D., Boveroux P., Garweg C., Lambermont B., Phillips C., Luxen A., Moonen G., Bassetti C., Maquet P., Laureys S. *Human Brain Mapping* 2009: 30, 393-400

V. Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. Schnakers C., Ledoux D., Majerus S., Damas P., Damas F., Lambermont B., Lamy M., Boly M., Vanhaudenhuyse A., Moonen G., Laureys S. *Brain Injury* 2008: 22 (12), 926-31

VI. Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. Schnakers C., Perrin F., Schabus M., Hustinx R., Majerus S., Moonen G., Boly M., Vanhaudenhuyse A., Bruno MA., Laureys S. *Neurocase* 2009: 25, 1-7

VII. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. Schnakers C., Vanhaudenhuyse A., Giacino J., Ventura M., Boly M., Majerus S., Moonen G., Laureys S. *BMC Neurology* 2009: 21, 9:35

VIII. Measuring the effect of amantadine in chronic anoxic minimally conscious state. Schnakers C., Hustinx R., Vandewalle G., Majerus S., Moonen G., Boly M., Vanhaudenhuyse A., Laureys S. *Journal of Neurology Neurosurgery and Psychiatry* 2008: 79, 225-7

IX. Voluntary brain processing in disorders of consciousness. Schnakers C., Perrin F., Schabus M., Majerus S., Ledoux D., Damas P., Boly M., Vanhaudenhuyse A., Bruno MA., Moonen G., Laureys S. *Neurology* 2008: 71, 1614-20

X. A French validation study of the Coma Recovery Scale-Revised (CRS-R). Schnakers C., Majerus S., Giacino J., Vanhaudenhuyse A., Bruno MA., Boly M., Moonen G., Damas P., Lambermont B., Lamy M., Damas F., Ventura M., Laureys S. *Brain Injury* 2008: 22, 786-92

XI. Brain function in physiologically, pharmacologically, and pathologically altered states of consciousness. Boveroux P., Bonhomme V., Boly M., Vanhaudenhuyse A., Maquet P., Laureys S. *International Anesthesiology Clinics* 2008: 46, 131-46

XII. Consciousness in the Locked-in Syndrome. Gosseries O., Bruno MA., Vanhaudenhuyse A., Laureys S., Schnakers C. *The Neurology of Consciousness*, S. Laureys & G. Tononi, 2008 Edition: Elsevier: 191-203

XIII. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Schnakers C., Chatelle C., Vanhaudenhuyse A., Majerus S., Ledoux D., Boly M., Bruno MA., Boveroux P., Demertzi A., Moonen G., Laureys S. *Pain* 2010: 148(2), 215-9

XIV. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. Demertzi A., Schnakers C., Ledoux D., Chatelle C., Bruno MA., Vanhaudenhuyse A., Boly M., Moonen G., Laureys S. *Progress in Brain Research* 2009: 177, 329-38

XV. Reaching across the abyss: recent advances in functional magnetic resonance imaging and their potential relevance to disorders of consciousness. Soddy A., Boy M., Nor Y., Noirhomme Q., Vanhaudenhuyse A., Demertzi A., Arzi A., Ovadia S., Stanziano M., Papa M., Laureys S., Malach R. *Progress in Brain Research* 2009: 177, 261-74

ABREVIATIONS

ALIS	Association pour Locked-In Syndrome
BAEPs	Brainstem Auditory Evoked Potentials
BCI	Brain Computer Interfaces
BOLD	Blood Oxygen Level Dependent
Cho	Choline
Cr	Créatinine
CRS-R	Coma Recovery Scale-Revised
CSI	Chemical Shift Imaging
DTI	Diffusion Tensor Imaging
EEG	Electroencéphalographie
FOUR	Full Outline of UnResponsiveness scale
FSL	Functional MRI of the Brain Software Library
GCS	Glasgow Coma Scale
GFAP	Acide Protéique Fibrillaire Glial
GLS	Glasgow Liège Scale
GOS	Glasgow Outcome Scale
ICA	Independent Component Analysis
IRM	Imagerie par Résonance Magnétique
IRMf	Imagerie par Résonance Magnétique fonctionnelle
La	Lactate
MLAEPs	Middle-Latency Auditory-Evoked Potentials
MMN	Mismatch Negativity
MRS	Magnetic Resonance Spectroscopy
NAA	*N*-acétylaspartate
NSE	Enolase Neurospécifique
PES	Potentiels Evoqués Somesthésiques
PV+	Valeur prédictive positive pour un degré de récupération favorable
PV-	Valeur prédictive positive pour un mauvais degré de récupération
ROI	Region of Interest
SMART	Sensory Modality Assessment and Rehabilitation Technique scale
SPM	Statistical Parametric Mapping
Sp+	Valeur de spécificité pour une récupération favorable
Sp-	Valeur de spécificité pour une mauvaise récupération
SVS	Single Voxel Spectroscopy
TEP	Tomographie à Emission de Positons
WHIM	Wessex Head Injury Matrix scale
WNSSP	Western Neuro Sensory Stimulation Profile scale

REMERCIEMENTS

Je souhaite remercier toutes les personnes qui ont permis la réalisation de ce travail.

Mes remerciements particuliers à mes promoteurs, Steven Laureys et Serge Brédart, qui m'ont donné l'opportunité de me lancer dans cette aventure qu'est la recherche et qui ont toujours été de bons conseils pour me faire évoluer. Merci à Steven pour sa confiance et sa patience. Merci aussi de croire en tous les « jeunes » de ton équipe.

Je voudrais aussi remercier les Professeurs André Luxen, Gustave Moonen, Pierre Maquet et Christophe Phillips qui, chacun à leur manière, m'ont soutenue, conseillée et aidée. Merci à Marie-Elisabeth Faymonville qui a toujours eu des paroles justes, encourageantes et réconfortantes.

Merci à tous les membres du Coma Science Group. Un merci particulier à Caroline Schnakers qui m'a aidée à faire mes premiers pas avec les patients et qui m'a appris avec beaucoup de patience tout ce qui relève du comportemental, et à Mélanie Boly qui a été une formatrice très patiente lors de mes durs combats avec Matlab et SPM et qui n'a jamais failli à sa devise « c'est en forgeant que l'on devient forgeron ! ». Merci à Marie-Aurélie Bruno, Olivia Gosseries, Pierre Boveroux, Athena Demertzi, Murielle Kirsh, Jean-Flory Tshibanda, Didier Ledoux, Grégory Hans, Séverine Lauwick, Mélanie et Caroline qui m'ont énormément aidée dans l'acquisition et l'analyse des données reprises dans cette thèse. Merci également à Marie Thonnard, Camille Chatelle, Quentin Noirhomme, Rémy Lehembre et Andrea Soddu pour leur aide précieuse dans notre travail quotidien.

Merci à tous les membres du service de Neuroimagerie du CHU Sart Tilman, particulièrement à Jacques Trenteseaux qui ne se ménage jamais pour nous faciliter la vie ; à Jean-Marc Léonard qui répond toujours présent à nos appels ; mais aussi à Nathalie, Cécile, Yulia, Catherine, Sabine, Arnaud, Florence et Youssef.

Merci à tous les médecins des Soins Intensifs qui nous permettent de travailler au sein de leur unité, particulièrement aux Docteurs Canivet, Massion, Ledoux, Piret, Lambermont, Damas et Lancelloti. Merci à tous les médecins et aux infirmières de Neurologie et Neurochirurgie, ainsi qu'à Mme Arena pour leur aide. Merci aussi à tous les anesthésistes qui m'ont aidée dans l'acquisition des données au CHU, particulièrement Claude Hallet, Julie Jastrowicz, Gaetane Hick et Robert Fontaine. Merci à Mme van der Kaa et Mr Vincent pour leur investissement dans nos projets.

Merci à toutes les personnes du Centre de Recherches du Cyclotron, particulièrement Eric Salmon, Fabienne Colette, Steve Majerus, Alain Plenevaux, Christina Schmidt, Virginie

Sterpenich, Yves Leclerc, Steffen Gais, Dorothée Feyers, Martin Desseilles et Manuel Schabus pour leur aide et soutien. Un merci spécial à Christian Degueldre qui s'arrache les cheveux avec nos ordinateurs capricieux, Annick Claes et Brigitte Herbillon qui font que ça « tourne » au CRC.

Merci particulièrement à Jonathan qui a eu la patience de me supporter pendant ces 3 ans et demi, d'accepter mes horaires parfois farfelus, mes sautes d'humeur liées au stress, qui n'a jamais cessé de m'encourager et de croire en moi et qui a toujours été là pour me remonter le moral.

Je voudrais aussi remercier Mariette qui, grâce à ces ondes de courage, m'a aidée à aller jusqu'au bout de cette thèse. Merci pour son soutien à toutes épreuves, d'avoir supporté mes larmes et d'avoir rit à mes « bonnes » blagues. *Le bout du tunnel n'est pas très loin…*

Mille mercis à mes parents, Christian et Anne-Marie, qui dès le début m'ont poussée à toujours aller plus loin et n'ont jamais cessé d'y croire ; mes sœurs Cosmina, Anouk, Alisson, Alinoë et Ioana, qui ont été les petites étoiles de ce chemin parsemé d'embûches ; Marraine pour sa soupe énergisante ; ainsi que Sara, amie très précieuse et la tribu des petits et grands Belge pour leur bouffées d'oxygène.

Enfin, je remercie les familles et les patients qui nous permettent chaque jour d'avancer un peu plus dans nos travaux de recherche.

Ces travaux ont été financés par l'Action de Recherche Concertée ARC 06/11-340, les Fonds de la Recherche Scientifique belge (FRS); la Commission Européenne (Mindbridge, DISCOS, CATIA et DECODER); la Mind Science Foundation; la James McDonnell Foundation; la Fondation Médicale Reine Elisabeth.

RESUME

Suite à un accident cérébral grave, qu’il soit traumatique ou hypoxique-ischémique, les patients peuvent évoluer d’un coma (patient non-éveillable et inconscient) vers un état végétatif (patient éveillé mais inconscient), un état de conscience minimale (patient éveillé et conscient, mais non-communiquant), ou un locked-in syndrome (patient éveillé, conscient, mais ne pouvant exprimer cette conscience que par le biais de mouvements oculaires) (Vanhaudenhuyse et al., 2009a). Notre but est de mettre au point des techniques permettant de détecter des signes de conscience chez ces patients incapables de communiquer, que ce soit par des évaluations comportementales, l’électroencéphalographie ou la neuroimagerie.

Etudes comportementales : Actuellement, malgré les nouveaux critères de conscience proposés par Giacino et al. en 2002, nous avons pu démontrer que jusqu’à 40% des patients étaient diagnostiqués comme étant en état végétatif, alors qu’ils étaient en réalité en état de conscience minimale (Schnakers, Vanhaudenhuyse et al., 2009b). Nos travaux ont mis en évidence que l’absence d’outil d’évaluation de la conscience standardisé pouvait expliquer la difficulté à détecter des signes de conscience. Nous avons démontré que la poursuite visuelle, qui est un des premiers signes de conscience réapparaissant chez les patients récupérant de l’état végétatif, était significativement mieux détectée lorsqu’elle était évaluée à l’aide d’un miroir (Vanhaudenhuyse et al., 2008c). L’absence de consensus sur la signification de certains comportements, en termes de conscience, peut également être à la source de problèmes diagnostiques. Nous avons, par exemple, démontré que le clignement à la menace visuelle, comportement ambigu de conscience, était compatible avec le diagnostic d’état végétatif et qu’il n’avait pas de valeur pronostique de récupération de conscience (Vanhaudenhuyse et al., 2008a).

Marqueurs électrophysiologiques : Distinguer un comportement volontaire d’un comportement réflexe reste difficile, ce qui nous pousse à étudier d’autres techniques permettant d’obtenir des marqueurs objectifs de conscience. Nous avons souligné l’intérêt des potentiels évoqués de courte latence comme marqueurs d’un mauvais pronostic, ainsi que des potentiels évoqués cognitifs pour évaluer la récupération d’une conscience et les fonctions cognitives résiduelles des patients en coma et post-coma (Vanhaudenhuyse et al., 2008b).

Neuroimagerie fonctionnelle et structurelle : Par l’Imagerie par Résonance Magnétique fonctionnelle (IRMf), nous avons pu mettre au point différents paradigmes d’aide au diagnostic d’état de conscience altérée de ces patients. L’étude du réseau du mode par défaut, c’est-à-dire de l’ensemble des régions cérébrales activées lorsque nous sommes au

repos et éveillés (précunéus, cortex mésio-frontal, jonctions temporo-pariétales), nous a permis de développer un outil facile à appliquer en routine clinique. Nous avons mis en évidence une corrélation négative non-linéaire entre la connectivité au sein du réseau du mode par défaut et le degré de conscience des patients (coma, état végétatif, état de conscience minimale et locked-in syndrome – Vanhaudenhuyse et al., 2010b). Par ailleurs, en collaboration avec l'équipe du *MRC Cognition and Brain Sciences Unit* de Cambridge, nous avons appliqué des paradigmes actifs en IRMf, durant lesquels 54 patients devaient réaliser activement des tâches cognitives (s'imaginer jouer au tennis, s'imaginer visiter sa maison). Sur 23 patients diagnostiqués comme étant en état végétatif, 4 d'entre eux (17%) étaient capables de moduler volontairement leur activité neuronale (Monti & Vanhaudenhuyse et al., 2010). De plus, ce paradigme a permis à un de ces patients, chez qui aucune communication n'était possible, de répondre à l'aide d'un code *oui* (imaginez jouer au tennis) / *non* (imaginez visiter votre maison) à des questions autobiographiques. Cependant, ce type de méthode est difficilement utilisable au quotidien. Dès lors, nous développons des interfaces cerveau-ordinateur transportables grâce au projet européen WF7 DECODER. Une de ces techniques de communication a pu être proposée par la modulation du pH salivaire chez un sujet sain (Vanhaudenhuyse et al., 2007a). Enfin, dans le cadre d'études multicentriques dirigées par le Pr. Louis Puybasset (Hôpital de la Pitié-Salpétrière, Paris), nous avons mis en évidence l'intérêt diagnostique et pronostique de séquences telles que l'imagerie par tenseur de diffusion et la spectroscopie (Tshibanda & Vanhaudenhuyse et al., 2009 ; 2010).

Au terme de ce travail, nous proposons des perspectives de nouvelles études à entreprendre afin d'améliorer les évaluations comportementales, mais aussi les paradigmes d'acquisition en IRM et en EEG que nous avons à notre disposition. Notre projet est de développer des recherches translationnelles validées pour une application clinique individuelle. Nous espérons que cette approche multimodale permettra d'améliorer la prise en charge des patients sévèrement cérébrolésés qui sont toujours un véritable défi pour le corps médical, mais aussi d'accroître nos connaissances sur la conscience humaine.

SUMMARY

Survivors of severe traumatic or hypoxic-ischemic brain damage classically go through different clinical entities such as coma (unarousable unconsciousness), vegetative state (characterized by wakefulness without awareness), minimally conscious state (minimal but definite evidence of awareness without communication) or locked-in syndrome (fully aware but unable to move or speak) (Vanhaudenhuyse et al., 2009a). Our goal is to improve and develop methods to detect consciousness in these non-communicative patients by using bedside behavioral examinations and para-clinical electroencephalography or neuroimaging techniques.

Behavioral examination: Bedside assessment is one of the main methods used to detect awareness in severely brain injured patients recovering from coma. However, our prospective multicentric study showed that up to 40% of patients may be diagnosed as vegetative while they are in reality in a minimally conscious state (Schnakers, Vanhaudenhuyse et al., 2009b). The failure to use standardized behavioral assessment tools and the absence of consensus about some clinical behaviors could explain the difficulty to identify signs of consciousness. For example, we showed that clinicians should use a mirror when evaluating visual pursuit, a behavior that is one of the first differentiating minimally conscious from vegetative patients (Vanhaudenhuyse et al., 2008c). Similarly, the blinking to visual threat remains an ambiguous clinical sign of consciousness. We showed that this behavior may be a common clinical feature of the vegetative state and that its presence does not necessarily herald consciousness nor recovery of consciousness in patients with severe brain injury (Vanhaudenhuyse et al., 2008a).

Electrophysiological markers: EEG methods offer objective assessment procedures and the possibility to determine whether an unresponsive patient is aware without explicit verbal or motor response. While early evoked-potentials are good prognosticators of bad outcome, cognitive evoked-potentials appear to be good predictors of favourable outcome and may be helpful to estimate the residual cognitive functions of comatose and post-comatose patients (Vanhaudenhuyse et al., 2008b).

Functional and structural neuroimaging: By using functional Magnetic Resonance Imaging (fMRI), we first studied the brain spontaneous activity and next used it to identify signs of consciousness and communication in these patients. Studies of default mode network in fMRI, i.e. brain regions encompassing precuneus, medial prefrontal cortex and temporo-parietal junctions which are more active at rest, are easy to perform and could have a

potentially broader and faster translation into clinical practice. We showed a negative non-linear correlation between default mode network connectivity and the level of consciousness of brain-damaged patients (ranging from coma, vegetative state, minimally conscious state to locked-in syndrome – Vanhaudenhuyse et al., 2010b). In collaboration with the *MRC Cognition and Brain Sciences Unit* in Cambridge, we applied active paradigms in fMRI (in which patients were asked to imagine playing tennis and visiting their house) in 54 patients. We showed that out of 23 vegetative patients, 4 (17%) were able to voluntary modulate their neuronal brain activity. Moreover, one of these patients, who was not able to behaviorally communicate, showed the ability to apply the imagery technique in order to answer accurately simple *yes* (imagine playing tennis) / *no* (imagine visiting your house) questions (Monti & Vanhaudenhuyse et al., 2010). However, this technique will not be useful in the daily life of these patients. Thus, we developed appropriate brain computer interfaces with our European partners of the WF7 DECODER project. For example, we showed that one of these methods could be the mental manipulation of salivary pH as a form of non-motor mediated communication (Vanhaudenhuyse et al., 2007a). Finally, international multi-centric studies leaded by Pr. Louis Puybasset (Pitié-Salpétrière Hospital, Paris) are validating the diagnostic and prognostic interests of MRI sequences such as diffusion tensor and spectroscopy imaging to evaluate the prognosis of recovery of severely brain injured patients (Tshibanda & Vanhaudenhuyse et al., 2009 ; 2010).

Future ongoing studies are continuing to improve our actual behavioral assessments, MRI and EEG measurements in disorders of consciousness. Our project is to validate translational research models that can be applied at the individual patient level. We hope that our multimodal and multidisciplinary approach will improve our medical care for brain-damaged patients suffering from disorders of consciousness and additionally shed some light to our understanding of the neural correlates of human consciousness.

INTRODUCTION

Tout ce que nous pouvons assurer, c'est qu'une théorie
scientifique n'est pas encore fausse
Karl Raimund Popper
1902-1994

Sur base des articles suivants :

Vegetative state.
Vanhaudenhuyse A., Boly M., Laureys S.
Scholarpedia 2009: 4, 4163

Detecting consciousness in minimally conscious patients.
Vanhaudenhuyse A., Schnakers C., Boly M., Perrin F., Brédart S., Laureys S.
Reanimation 2007: 16, 527-532

Locked-in syndrome and disorders of consciousness: how to detect consciousness?
Vanhaudenhuyse A., Bruno M.A., Schnakers C., Boly M., Boveroux P., Moonen G., Perrin F., Pellas F., Pantke KH., Laureys S.
In: Pellas, F., Kiefer, C., Weiss, J., Pélissier, J. (Eds.), *Eveil de coma et états limites. Etats végétatifs, états pauci-relationnels et locked-in syndrome*. Masson, Issy-les-Moulineaux, 2007: pp. 109-116

Grâce à l'évolution des techniques de réanimation, de plus en plus de personnes survivent à un accident cérébral grave, qu'il soit traumatique ou anoxique. Alors que la majorité des patients récupèrent de leur coma dans les jours qui suivent l'accident, certains perdront totalement toute fonction cérébrale (mort cérébrale), tandis que d'autres passent par différents stades, tels que l'état végétatif, l'état de conscience minimale ou le locked-in syndrome, avant de récupérer partiellement ou totalement un état de conscience normale. Aujourd'hui, l'évaluation comportementale est l'outil principal pour établir un diagnostic d'état de conscience altérée chez ces patients (Majerus et al., 2005). Cependant, la pratique clinique démontre que détecter les signes de conscience au chevet du patient reste difficile (Andrews et al., 1996; Bruno et al., 2009; Childs et al., 1993; Schnakers, Vanhaudenhuyse et al., 2009b). 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. Dans ce travail, nous proposons tout d'abord de passer en revue les différents états de conscience altérée rencontrés après un coma (Vanhaudenhuyse et al., 2009a; 2007b; 2007c; Chatelle et al., 2010; Demertzi et Vanhaudenhuyse et al., 2008). Ensuite, nous présenterons nos différentes études comportementales (Schnakers, Vanhaudenhuyse et al., 2009b; Vanhaudenhuyse et al., 2008a; 2008c), électrophysiologique (Vanhaudenhuyse et al., 2008b) et de neuroimagerie (Monti & Vanhaudenhuyse et al., 2010; Vanhaudenhuyse et al., 2007a; 2010a; 2010b; Tshibanda & Vanhaudenhuyse et al., 2010; 2009) appliquées chez les patients en état de conscience altérée.

I. Définition clinique de la conscience

Depuis quelques années, l'engouement pour les phénomènes conscients a poussé les scientifiques et philosophes à proposer de nouvelles théories sur les mécanismes, les fonctions et la nature 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*. *Conscience* vient du latin *conscientia* composé du préfixe *con-* («avec») et *scientia* («science»). Comme le soulignent Damasio et Meyer (2009), la conscience est un phénomène subjectif consistant en une série de représentations mentales localisées dans un organisme et formulées selon la propre perspective de cet organisme. La conscience a deux composantes (Zeman, 2001): l'éveil (*arousal*) et le contenu de la conscience (*awareness*). Les critères de la première composante, l'éveil, sont simples à définir : ouverture des yeux, tonus musculaire et un électroencéphalogramme caractérisé par des fréquences rapides (pour une revue, voir, Damasio and Meyer, 2009). La modulation de l'état d'éveil dépend du tronc cérébral et de ses projections thalamiques et corticales (Steriade, 1996; Vogt and Laureys, 2005). 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 (Posner et al., 2007). Une personne consciente présentera des comportements traduisant des émotions, une capacité à être attentive et à s'orienter vers un stimulus spécifique et des comportements adaptés au contexte (Damasio and Meyer, 2009). La capacité d'attention est en général la preuve d'une conscience. Cependant, l'absence d'attention ne dénote pas systématiquement d'une absence de conscience, mais peut parfois simplement traduire l'état d'attention interne de la personne. Selon certains auteurs, c'est plutôt l'absence d'attention soutenue qui est un signe d'altération de la conscience. La capacité à interagir correctement selon le contexte implique que la personne est capable d'orienter son action selon le moment présent et en anticipant les conséquences futures. La présence de ces comportements contextualisés implique systématiquement une conscience. Cependant, la présence d'une conscience ne garantit pas une réponse comportementale systématiquement congruente avec le contexte.

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). Les patients en coma ou sous anesthésie générale ne sont ni éveillés, ni conscients. D'autres états pathologiques, tels que l'état végétatif, 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.

La conscience, telle que nous venons de la décrire (*awareness*), peut également être divisée en deux sous composantes : la *conscience de l'environnement* et la *conscience de soi* (James, 1890). 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 (Damasio and Meyer, 2009). Le point de départ d'une activité consciente consiste en la génération d'une représentation d'un objet ou d'un événement, grâce à une perception via les cinq sens. La seconde étape est la nécessité d'une conscience de soi dans le sens d'un savoir, permettant de comparer ces perceptions aux connaissances que l'individu a déjà acquises précédemment. La conscience doit donc être vue selon deux perspectives : une perspective externe – comportementale (expression de l'éveil, des émotions et de l'attention) et une perspective interne – cognitive (représentation d'un stimulus selon ses propres connaissances, son propre état mental – Damasio and Meyer, 2009). En l'absence de communication, comme c'est le cas chez les patients post-coma, nous sommes limités à l'observation des comportements liés à la perspective externe. La conscience dépend de l'intégrité fonctionnelle du cortex cérébral et de ses interactions sous-corticales, comme nous le verrons dans la suite de ce travail. Dans les études que nous présenterons, nous avons choisi de définir la conscience externe – de l'environnement – comme la perception consciente de l'environnement au travers de différentes modalités sensorielles (perceptions visuelle, auditive, somesthésique ou olfactive) ; et la conscience interne – de soi – comprenant l'ensemble des processus mentaux ne requerrant pas la médiation de stimuli externes ou sensoriels (par exemple, les pensées internes, les rêves éveillés, l'imagerie mentale, etc., pour une revue voir Lieberman, 2007).

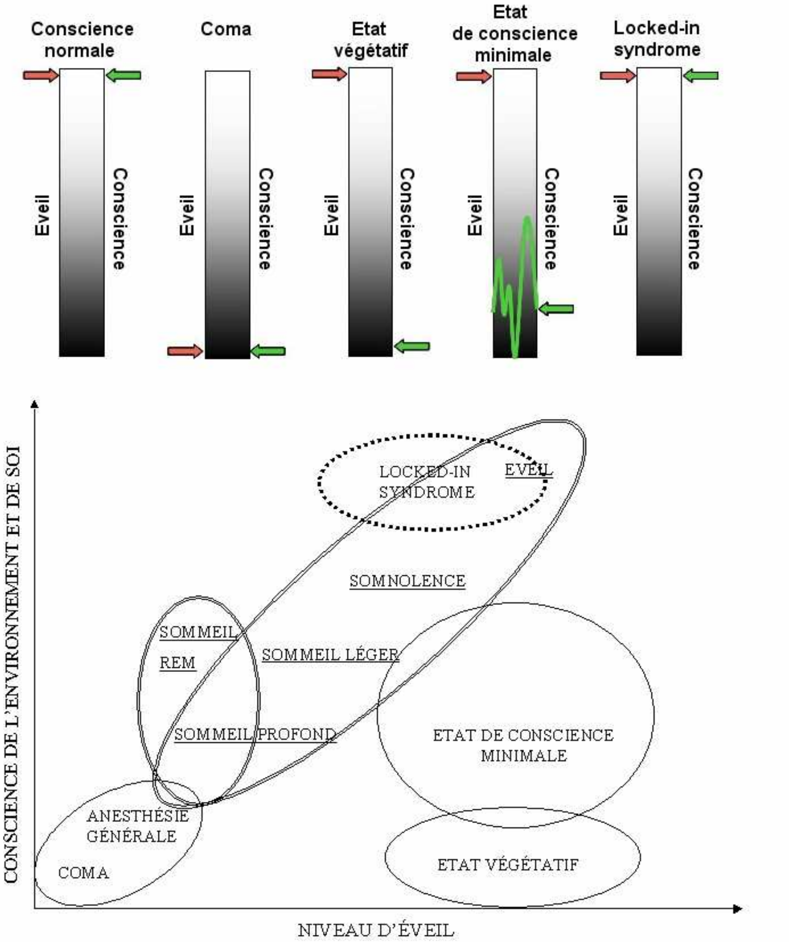


Figure 1 : Illustration des deux composantes de la conscience : le niveau de conscience (*arousal* / *wakefulness*) et le contenu de la conscience (*awareness*). (Adapté de Vanhaudenhuyse et al., 2007c, 2009a)

II. Définition des états de conscience altérée

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, grâce aux nouvelles techniques de réanimation et de ventilation artificielle, ces patients pouvaient être maintenus en vie à l'aide de machines. En 1959, les neurologues Mollaret et Goulon sont les premiers à mettre sur papier une discussion traitant des problèmes cliniques, électrophysiologiques et éthiques rencontrés chez les patient en mort cérébrale, précédemment appelés patients en coma dépassé (Mollaret and Goulon, 1959). Malheureusement, ce texte écrit en français n'a jamais été connu universellement. La définition officielle de la mort cérébrale fut proposée par *The Harvard Medical School Ad Hoc Comittee* (1968) qui précisa qu'un patient ne pouvait être diagnostiqué comme étant en mort cérébrale que s'il démontrait une cessation permanente et irréversible de toutes ses fonctions neurologiques. Quelques années plus tard, cette définition est affinée par Bernat (2009a) qui propose qu'un patient ne soit déclaré en mort cérébrale que lorsque toutes ses fonctions cérébrales cliniques aient cessées de fonctionner de manière permanente, indépendamment d'une ventilation et une circulation artificielles (Tableau 1). Le diagnostic de mort cérébrale est donc basé sur la perte totale 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, électrolytes et endocriniens (Bernat, 2009a; Laureys, 2005b). Des mouvements très ralentis et générés par une activité spinale résiduelle sont observés chez un tiers des patients en mort cérébrale : extension réflexe des doigts, flexion réflexe des orteils, signe de Lazare et myokimies faciales (Saposnik et al., 2000; 2005). Par ailleurs, les patients en mort cérébrale ne démontrent jamais d'expression faciale ni de vocalisation (Laureys, 2005b). Selon les guidelines, une réévaluation dans les six à vingt-quatre heures est conseillée afin de confirmer le diagnostic (Posner et al., 2007; The Quality Standards Subcommittee of the American Academy of Neurology, 1995; Wijdicks, 2002). Des examens par électroencéphalographie (EEG), potentiels évoqués, angiographie, doppler trans-crânien ou scintigraphie cérébrale sont nécessaires afin de confirmer les tests neurophysiologiques. Les causes principales de la mort cérébrale peuvent être un traumatisme crânien, une hémorragie sous-arachnoïdienne anévrismale, une hémorragie intracrânienne, un accident vasculaire cérébral ischémique, une encéphalopathie hypoxique-ischémique, ou une nécrose hépatique fulminante (Posner et al., 2007). L'EEG d'un patient en mort cérébrale est caractérisé par une absence d'activité électro-corticale. Quant à la neuroimagerie fonctionnelle, elle démontre une absence totale des fonctions neuronales dans l'entièreté du cerveau du patient (pour une revue, voir Laureys et al., 2004a). Au niveau du pronostic, des études ont démontré qu'aucun patient déclaré en mort cérébrale n'avait jamais récupéré (Bates et al., 1977) et que si les réflexes du tronc cérébral ne réapparaissaient pas dans l'heure suivant l'accident, aucune récupération n'était à espérer (Jorgensen, 1973).

Définir la mort cérébrale est étroitement lié à la problématique du don d'organe. En effet, le patient doit être déclaré comme étant en mort cérébrale avant que la procédure de don d'organe ne puisse être autorisée. Ethiquement, les chirurgiens chargés de la transplantation d'organe sont exclus de la procédure diagnostique du patient. Le protocole pour « le don d'organe après une mort cardiaque » (or *DCD - donation after cardiac death*, University of Pittsburgh Medical Center policy and procedure manual, 1993) 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 (Bernat, 2006).

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), causée par une lésion dans le système activateur réticulaire, ainsi qu'une absence de conscience de soi et de l'environnement (Posner et al., 2007). Afin de distinguer le coma d'une syncope, une commotion ou d'un autre état de perte de conscience transitoire, le coma doit durer au moins une heure. Le coma peut se prolonger de quelques jours à quelques semaines. Les patients évolueront progressivement dans les deux à quatre semaines en passant par différents stades tels que l'état végétatif, l'état de conscience minimale ou le locked-in syndrome (Figure 1). 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 (Posner et al., 2007). Après trois jours d’observation, l’absence des réflexes pupillaires et/ou cornéens, l’absence de réponses motrices ou stéréotypées lors de stimulations nociceptives, un EEG isoélectrique, l’absence bilatérale de réponses corticales aux potentiels évoqués somesthésiques (PES), et (pour les étiologies anoxiques) des marqueurs biochimiques comme un taux important d'énolase neurospécifique (NSE), sont reconnus comme étant de mauvais pronostic (Laureys et al., 2008). L’ensemble des travaux ayant étudié le pronostic des patients en coma après un accident traumatique démontrent que des réponses motrices anormales aux stimuli nociceptifs (flexion/extension stéréotypées), 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 (pour une revue, voir Posner et al., 2007). 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 (Sanchez-Pena et al., 2008), ainsi qu’une cause ischémique-vasculaire ou hémorragique sont prédictifs d’un mauvais pronostic (pour une revue, voir Posner et al., 2007). Par ailleurs, le pronostic des patients dont l’étiologie est traumatique est démontré comme étant significativement meilleur que celui des patients dont l’étiologie est anoxique (Laureys et al., 2010; Posner et al., 2007). Le taux de mortalité d’un patient en coma varie de 40 à 88% selon que l’étiologie soit anoxique ou traumatique (Posner et al., 2007).

3. *Etat végétatif*

Après quelques jours à quelques semaines, le patient peut évoluer et ouvrir les yeux. Quand cette récupération d’un cycle veille-sommeil s’opère, sans être accompagnée d’aucun signe de conscience, le patient est diagnostiqué comme étant en état végétatif (Tableau 1 – The Multi-Society Task Force on PVS, 1994). Jennet et Plum (1972) ont choisit 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 d’interactions sociales ; vegetative – organisme capable de croître et de se développer mais dépourvu de sensation et de pensée*. Le patient en état végétatif ne présente que des comportements dits réflexes, aucun comportement volontaire ne peut donc être observé. L'état végétatif peut être un état transitoire, dans ce cas le patient évoluera vers un état de conscience minimale ou récupérera une conscience normale. L'état végétatif peut également progresser vers un état chronique que l'on nomme alors *état végétatif permanent*. On parlera également *d'état végétatif persistant* lorsque le patient a passé un délai d'un mois. Cependant, ces deux termes – *permanent, persistant* – abréviés de la même manière *PVS* sont souvent confondus et utilisés à mauvais escient (Laureys et al., 2000a). Il est aujourd'hui recommandé d'éviter le terme *persistant*. La plupart des patients en état végétatif récupèrent un certain degré de conscience dans le mois qui suit l'accident. Cependant, si le patient est toujours en état végétatif trois mois après un accident non-traumatique ou un an après un accident traumatique, ses chances de récupération sont proches de zéro (The Multi-Society Task Force on PVS, 1994). Des cas rares de récupération après ces délais ont déjà été rapportés dans la littérature (Childs and Mercer, 1996). S'il n'y a pas eu de signe de récupération dans les trois ou douze mois après l'accident (selon l'étiologie), le patient est déclaré en état végétatif permanent (Jennett, 2005; Laureys et al., 2004a). Les chances de récupération d'un patient en état végétatif dépendent de son âge lors de l'accident, de l'étiologie – les patients dont l'étiologie est traumatique ont de meilleures chances de récupérer que les patients dont la cause est non-traumatique (Laureys et al., 2010), ainsi que du temps passé en état végétatif. De plus, 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 est traumatique (Carpentier et al., 2006; Kampfl et al., 1998).

L'EEG des patients en état végétatif est caractérisé par un ralentissement généralisé de l'activité électrique cérébrale. Chez les patients en état végétatif, 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 sont sévèrement atteintes (Owen et al., 2009). Grâce à des études réalisées en tomographie à émission de positons (TEP), Levy et al. (1987) ont été les premiers à démontrer que les patients en état végétatif souffraient d'une diminution importante du métabolisme cérébral global, allant jusqu'à 40 à 50% en dessous de celui observé chez des sujets sains éveillés. Ces résultats ont été confirmés par d'autres travaux réalisés avec des patients en état végétatif d'étiologie et de durée différentes (De Volder et al., 1990; Laureys et al., 1999b; Rudolf et al., 1999; Tommasino et al., 1995). Une diminution similaire du métabolisme cérébral est également observée en sommeil (Maquet et al., 1990) et chez des patients sous anesthésie générale (Alkire et al., 1995; 1997; 1999). Cependant, le métabolisme globale seul ne peut expliquer l'absence de conscience chez les patients en état végétatif, puisque certains patients qui récupèrent de leur état végétatif ne démontrent pas de changement au niveau de leur activité cérébrale globale mesurée en TEP (Laureys et al., 1999b) et que certains sujets sains éveillés présentent une activité cérébrale globale similaire à celle des patients en état végétatif (Laureys, 2005a). En réalité, l'état végétatif se caractérise par un dysfonctionnement, non pas de l'entièreté du cerveau, mais plutôt d'un réseau 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 (Laureys et al., 1999a; 2004a). De plus, l'activité du précunéus ainsi que du cortex cingulaire postérieur permet de différencier l'état végétatif de l'état de conscience minimale, que nous définirons ci-après (Laureys et al., 2004b – le métabolisme cérébral de ces régions est plus élevé chez les patients en état de conscience minimale que chez les patients en état végétatif, mais plus bas que chez des sujets contrôles). De la même manière, une récente étude réalisée avec des patients traumatiques chroniques démontre que les régions fronto-basales médianes, préfrontales médianes, le précunéus et le thalamus étaient davantage hypométaboliques chez les patients en état végétatif que chez ceux en état de conscience minimale (Nakayama et al., 2006). Ces travaux mettent donc en évidence que la conscience résulte d'une connectivité fonctionnelle au sein du réseau fronto-pariétal et avec le thalamus. En effet, une déconnection fonctionnelle cortico-corticale et thalamo-corticale a été identifiée chez les patients en état végétatif (Laureys et al., 2000c; 1999a).

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. La perception de ce type de stimuli nécessite une capacité de conscience qui est, par définition, absente chez ces patients. Cependant, l'absence de réactions comportementales ne peut pas être considérée comme une preuve absolue d'absence de conscience (Bernat, 1992; McQuillen, 1991). Les études en TEP, ainsi que celles réalisées en imagerie par résonance magnétique fonctionnelle (IRMf) ont permis de démontrer une activation des cortex primaires sensoriels de bas niveau totalement déconnectée des réseaux corticaux associatifs de haut niveau chez les patients en état végétatif, que ce soit lors de stimulations auditives (Boly et al., 2005; 2004; Coleman et al., 2009; 2007; Di et al., 2007; Fernandez-Espejo et al., 2008; Laureys et al., 2000b; Owen et al., 2002; Staffen et al., 2006), somato-sensorielles (Boly et al., 2005) ou visuelles (Menon et al., 1998; Owen et al., 2002). Ces résultats suggèrent que la perception des stimuli environnants est altérée chez les patients en état végétatif.

Il est important de souligner les différences entre la mort cérébrale et l'état végétatif. L'état végétatif peut être partiellement ou totalement réversible. De plus, alors que les patients en état végétatif ouvrent les yeux, les patients en mort cérébrale ne présenteront jamais ce type de comportement. Les patients en état végétatif font preuve de comportements plus complexes que les patients en mort cérébrale, même si ceux-ci restent non-conscients : mouvements du tronc, des membres, de la tête, des yeux sans signification spécifique (pour une revue, voir Laureys, 2005b). Des sourires, des pleurs, des grognements (non adaptés au contexte) peuvent être observés chez les patients en état végétatif, alors qu'aucune expression faciale n'a jamais été observée en mort cérébrale. Enfin, contrairement aux patients en mort cérébrale, les patients en état végétatif peuvent avoir une respiration spontanée, sans aucune ventilation artificielle et ont des réflexes du tronc cérébral et des fonctions hypothalamiques préservées. Par ailleurs, le métabolisme cérébral global de l'état végétatif n'est pas compatible avec celui de la mort cérébrale.

4. *Etat de conscience minimale*

Certains patients sévèrement cérébrolésés démontrent des signes limités mais clairs et reproductibles de conscience de leur environnement. L'état de conscience minimale se distingue de l'état végétatif par la présence de comportements reproductibles et soutenus de conscience (Tableau 1). Ces comportements doivent se manifester sur période assez longue afin de ne pas les confondre avec des mouvements réflexes (Giacino et al., 2002). Un patient en état de conscience minimale est incapable d'exprimer ses pensées et son ressenti, mais démontre 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.), verbalisations intelligibles. Tout comme l'état végétatif, 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 cela a été démontré par le patient américain Terry Wallis (Voss et al., 2006). L'émergence de l'état de conscience minimale est caractérisée par la présence fiable et consistante d'une communication fonctionnelle ou de l'utilisation fonctionnelle de deux objets de la vie courante (un peigne et une tasse, par exemple - Giacino et al., 2002) (Figure 2). Les critères de l'état de conscience minimale étant encore assez récents, il existe peu d'études réalisées avec ces patients.

Toutefois, des données préliminaires nous permettent déjà de dire que les patients en état de conscience minimale dont l'étiologie est traumatique ont de meilleures chances de récupérer une communication fonctionnelle que ceux dont l'étiologie est non-traumatique (Laureys et al., 2010). Il semblerait que le pronostic de récupération des patients en état de conscience minimale soit plus favorable que celui des patients en état végétatif (Giacino, 1997; Laureys et al., 2010). Des études proposent que la réapparition d'une poursuite visuelle pourrait prédire la récupération progressive d'autres signes de conscience (Ansell and Keenan, 1989; Giacino and Kalmar, 1997; Shiel et al., 2000).

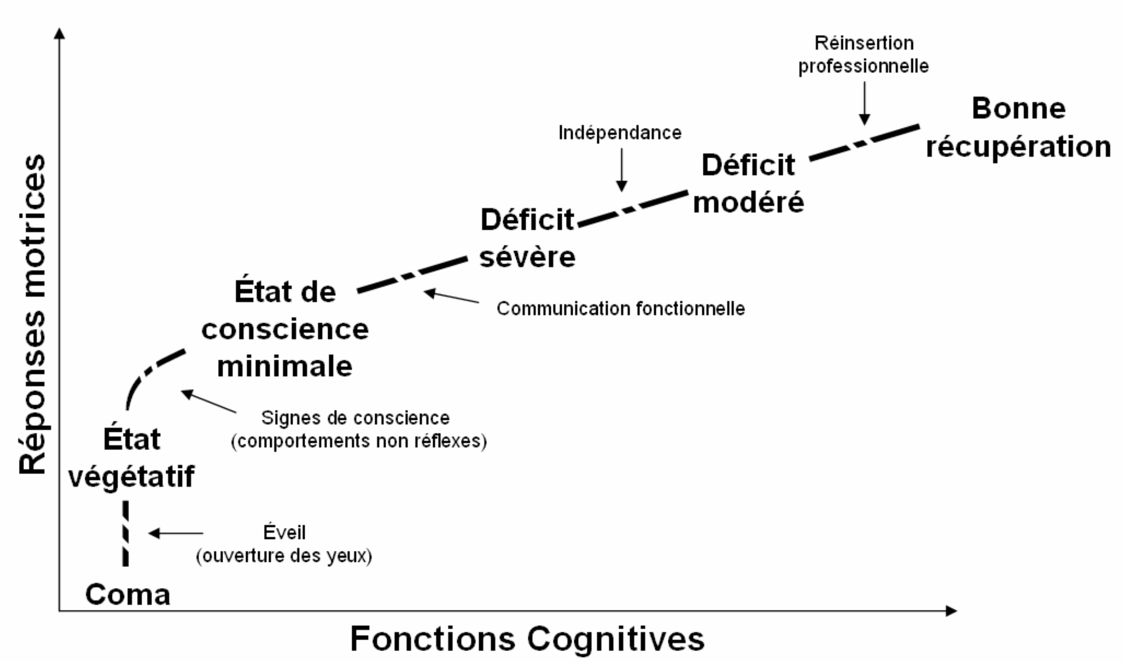


Figure 2 : Schéma représentant l'évolution classique du coma à une récupération fonctionnelle. (Adapté de Vanhaudenhuyse et al., 2009a)

L'EEG de patients en état de conscience minimale démontre un ralentissement général de l'activité électrique du cerveau. Les études réalisées en TEP ont démontré que les activations régionales du précunéus et du cortex cingulaire antérieur semblent être la clé pour différencier un patient conscient d'un patient inconscient (Laureys et al., 2004a). Contrairement à l'état végétatif, 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 (Boly et al., 2005) et nociceptives (Boly et al., 2008a). Des stimuli auditifs ayant une valence émotionnelle (tels que les cris d'un bébé – Laureys et al., 2004b, ou un récit narré par la mère du patient – Schiff et al., 2005) 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.

5. Locked-in syndrome

> *Je suis ce que l'on surnomme vulgairement un légume. A trois détails près non négligeables : j'ai toute ma tête, je sens les mains qui me touchent, et j'ai découvert que mes paupières n'étaient pas seulement deux peaux qui protègent les globes oculaires et qui accueillent des fards multicolores.*
>
> (Laetitia Bohn-Derrien, 2005)

Le locked-in syndrome doit être considéré comme une pathologie à part des états de conscience altérée. C'est à Plum et Posner (1966) que l'on doit l'introduction du terme *locked-in syndrome* pour décrire ces patients dont le tableau clinique est défini comme « 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 (voir également Schnakers et al., 2008c), une aphonie ou une hypophonie sévère, une quadriplégie ou une quadriparésie, et une communication basée principalement sur les mouvements oculo-palpébraux » (American Congress of Rehabilitation Medicine, 1995 – Tableau 1). Cette pathologie peut être divisée en trois catégories selon l'étendue du handicap moteur et verbal (Bauer et al., 1979) : le locked-in syndrome classique est caractérisé par une immobilité totale à l'exception du mouvement vertical des yeux et du clignement des paupières ; le locked-in syndrome incomplet bénéficie de quelques reliquats de motricité volontaire ; le locked-in syndrome complet 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 décédant dans les quatre premiers mois après l'accident (Patterson and Grabois, 1986). Les informations de la base de données de l'Association pour Locked-In Syndrome (ALIS) indiquent que les patients qui survivent sont plus jeunes lors de l'atteinte, que les patients qui décèdent (Gosseries et al., 2009). La durée de vie moyenne est de 6±4 ans (intervalle entre 14 jours et 29 ans – Gosseries et al., 2009). Même s'il existe de rares cas de récupération complète d'un locked-in syndrome (Bohn-Derrien, 2005), la majorité des patients souffrent de déficits moteurs sévères. Afin d'améliorer leur capacité à interagir avec leur entourage et donc d'améliorer leur qualité de vie, divers systèmes d'interfaces cerveau/ordinateur ont été et sont toujours en cours de création (pour une revue, voir Kübler, 2009).

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. 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 centro-pontine, une encéphalite, un abcès de la protubérance, une intoxication au niveau du tronc cérébral, une réaction à un vaccin ou une hypoglycémie prolongée. Des cas de locked-in syndromes complets temporaires ont été signalés après un syndrome de Guillain Barré ou des polyneurophaties post-infectieuses sévères. Des cas de locked-in réversibles peuvent également être observés lorsque le patient reçoit un curare avec une dose insuffisante d'anesthésiants (pour des revues, voir Bruno et al., 2008; Laureys et al., 2005a). Les résultats d'enregistrements EEG chez des patients atteints du locked-in syndrome sont très hétérogènes. En effet, certaines études ont démontré que les tracés EEG de ces patients étaient normaux ou légèrement plus lents, avec une activité alpha réactive et normalement distribuée (Bassetti et al., 1994; Markand, 1976) ; alors que d'autres notent un ralentissement diffus du signal EEG chez la moitié des patients (Patterson and Grabois, 1986) ; ou encore un rythme alpha non réactif aux stimuli multimodaux (Gutling et al., 1996; Jacome and Morilla-Pastor, 1990). 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 (Laureys et al., 2004a). 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 (Leon-Carrion et al., 2002). Une hyperactivité significative de l’amygdale est également observée chez les patients locked-in syndrome 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 (Calder et al., 2001). 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. Il est donc nécessaire de diagnostiquer correctement et le plus rapidement possible le locked-in syndrome afin d’adapter la prise en charge thérapeutique aussi bien médicamenteuse que comportementale.

Tableau 1 : Critères diagnostiques des états de conscience altérée et du locked-in syndrome. (Vanhaudenhuyse et al., 2009a)

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
Etat végétatif
• 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 • Préservation variable des réflexes spinaux et crâniens
Etat de conscience minimale
Evidence 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 - atteinte d'un objet placé dans le champ visuel - préhension d'un objet adaptée à ses forme et taille - vocalisations ou gestes en réponses à une question • Réponse à des commandes simples • Réponses oui/non verbales ou non-verbales (indépendantes de leur justesse) • Verbalisations intelligibles
Emergence de l'état de conscience minimale
Récupération d'un des comportements suivants : • Communication fonctionnelle • Capacité à utiliser fonctionnellement des objets
Loked-in syndrome
• Ouverture des yeux soutenue (un ptôsis bilatéral doit être exclut 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

OUTILS CLINIQUES D’EVALUATION DE LA CONSCIENCE

Le doute est le commencement de la sagesse

Aristote

384-322 ACN

Sur base des articles suivants :

Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment.
Schnakers C., Vanhaudenhuyse A., Giacino J., Ventura M., Boly M., Majerus S., Moonen G., Laureys S.
BMC Neurology 2009: 9, 35

Assessment of visual pursuit in post-comatose states: use a mirror.
Vanhaudenhuyse A., Schnakers C., Brédart S., Laureys S.
Journal of Neurology Neurosurgery and Psychiatry 2008: 79, 223

Blink to visual threat does not herald consciousness in the vegetative state.
Vanhaudenhuyse A., Giacino J., Schnakers C., Kalmar K., Smart C., Bruno MA., Gosseries O., Moonen G., Laureys S.
Neurology 2008: 71 (17): 1374-5

Is there anybody in there? Detecting awareness in disorders of consciousness. Demertzi A., Vanhaudenhuyse A., Bruno MA., Schnakers C., Boly M., Boveroux P., Maquet P., Moonen G., Laureys S.
Expert Rev Neurother 2008: 8, 1719-1730

The Sensory Modality Assessment and Rehabilitation Technique (SMART): a behavioral assessment scale for disorders of consciousness.
Chatelle C., Schnakers C., Bruno MA., Gosseries O., Laureys S., Vanhaudenhuyse A.
Revue Neurologique 2010: in press

I. Echelles d’évaluation comportementale

Même si diverses technologies sont de plus en plus utilisées, l’évaluation clinique comportementale est la méthode principale pour détecter la conscience au chevet du patient (Majerus et al., 2005). C’est en 1974 que Teasdale et Jennett proposèrent la première échelle standardisée d’évaluation comportementale du coma : la *Glasgow Coma Scale – GCS*. Malgré son succès international, les cliniciens ont rapidement été confrontés aux limites de cette échelle (Jagger et al., 1983; Moskopp et al., 1995; Rowley and Fielding, 1991). Par exemple, la composante verbale ne peut être évaluée chez les patients intubés. L’information fournie s’en trouve dès lors tronquée (Murray et al., 1999). De plus, la GCS n’envisage pas l’évaluation des réflexes du tronc cérébral, ce qui entraîne une perte d’informations non négligeable dans le diagnostic et le pronostic des patients cérébrolésés. Cette lacune sera comblée par la *Glasgow Liège Scale* (Born, 1988). S’ensuivit ensuite le développement d’autres échelles. Récemment, la *Full Outline of UnResponsiveness scale – FOUR* (Wijdicks et al., 2005) a été validée et proposée pour remplacer la CGS. L’intérêt de la FOUR est que sa passation est courte et qu’elle peut être facilement utilisée dans les unités de soins intensifs (Schnakers et al., 2006). La FOUR a spécifiquement été développée pour détecter l’état végétatif, le locked-in syndrome et la mort cérébrale et n’inclut pas l’évaluation des fonctions verbales (Wijdicks et al., 2005). Par ailleurs, la FOUR évalue la poursuite visuelle, premier signe de conscience réapparaissant chez les patients en état de conscience minimale (Giacino et al., 2002). Enfin, la *Coma Recovery Scale-Revised – CRS-R*, proposée par Giacino et al. (2004) nous semble l’échelle la plus adaptée pour différencier les patients en état végétatif des patients en état de conscience minimale. La CRS-R a été créée sur base des critères de l’état de conscience minimale et a été démontrée comme étant significativement plus performante dans la détection des signes de conscience chez des patients non-communiquant que la GCS (Schnakers et al., 2006). Une version validée en français est désormais disponible (Schnakers et al., 2008b). La *Wessex Head Injury Matrix – WHIM*, est, quant à elle, utilisée pour évaluer l’évolution cognitive du patient grâce à des items d’une complexité croissante (Shiel et al., 2000). Enfin, la *Sensory Modality Assessment and Rehabilitation Technique – SMART* (Gill-Thwaites and Munday, 2004) a été créée par l’équipe de thérapie occupationnelle du Royal Hospital for Neuro-disability comme outil diagnostique et d’évaluation de la récupération des patients en état de conscience altérée. Cependant, aucune étude n’a actuellement été réalisée comparant la SMART à la CRS-R, échelle qui a pourtant montré sa sensibilité par rapport à d’autres échelles. 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 (Chatelle et al., 2010). Ces mêmes stimulations peuvent aussi être utilisées par la suite dans une phase de traitement. Le protocole de la SMART est précis et détaillé, ce qui lui procure une bonne fiabilité intra et inter juges (Gill-Thwaites and Munday, 2004). Un autre 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 est 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 (10) et le temps nécessaires 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 et ne permettent pas d’établir un diagnostic précis.

II. Diagnostic basé sur le consensus clinique comparé aux évaluations standardisées

Différencier un comportement volontaire d’un comportement réflexe, chez des patients incapables de communiquer, demeure un véritable défi. Il y a une dizaine d’années, 37 à 43% des patients étaient erronément diagnostiqués comme étant en état végétatif alors qu’ils présentaient en réalité des signe de conscience (en état de conscience minimale - Andrews et al., 1996; Childs et al., 1993). Dans une récente étude, nous avons démontré que le taux de diagnostic erroné d’état végétatif s’élevait toujours à 41%, et ce malgré l’introduction des nouveaux critères de l’état de conscience minimale en 2002 (Schnakers, Vanhaudenhuyse et al., 2009b). En effet, sur 103 patients étudiés (âge moyen 55±19 ans, 64 d’origine non-traumatique et 39 traumatique), 44 étaient diagnostiqués comme étant en état végétatif par le personnel médical (médecins, infirmières, logopèdes, ergothérapeutes, kinésithérapeutes). Sur ces 44 patients, une évaluation comportementale à l’aide de la CRS-R a permis de détecter des signes de conscience chez 18 d’entre eux (41%). Les résultats obtenus dans cette étude démontrent qu’un diagnostic erroné était plus souvent émis pour les patients chroniques (>4 semaines ; 14 sur 29, 48%) que pour les patients en stade aigu (<4semaines ; 4 sur 15 ; 27% ; $p<0.01$). Par ailleurs, sur 41 patients diagnostiqués en état de conscience minimale, 4 (10%) avaient émergé de leur état de conscience minimale (présence d’une communication fonctionnelle et/ou d’une utilisation fonctionnelle d’objets – Giacino et al., 2002). Enfin, sur les 18 patients dont le diagnostic était incertain selon l’équipe médicale, 16 (89%) démontraient des signes de conscience lors de l’évaluation avec la CRS-R. Les signes de conscience n’ayant pas été détectés par le corps médical étaient principalement d’ordre visuel (fixation et poursuite visuelles – Tableau 2).

Tableau 2 : Comportements considérés comme conscients selon la Coma Recovery Scale – Revised chez des patients diagnostiqués par le corps médical comme état végétatif (EV), état de conscience minimale (ECM), émergence de l’état de conscience minimale (E-ECM) ou d’un diagnostic incertain. (Schnakers, Vanhaudenhuyse et al., 2009b)

	Diagnostic émis par le corps médical		
Comportements	**EV**	**ECM**	**Incertain**
1 – Réponse à une commande verbale	4	*	4
2 – Réponse visuelle	8	*	6
3 – Réponse motrice automatique	1	*	1
4 – Localisation à la douleur	1	*	1
5 – Plusieurs critères d’ECM	4	*	4
6 – Communication	*	1	*
7 – Utilisation fonctionnelle d’objets	*	1	*
8 – Plusieurs critères d’E-EMCS	*	2	*

Les troubles moteurs ou langagiers, la présence d’une trachéotomie, la fluctuation du niveau d’éveil et de vigilance ou encore des réponses comportementales ambiguës sont autant de facteurs qui rendent les observations cliniques compliquées (Gill-Thwaites, 2006). Une mauvaise évaluation, ainsi qu’une mauvaise interprétation des comportements visuels traduisant une conscience (par exemple, la poursuite visuelle) sont aussi partiellement à l’origine de cette difficulté à émettre un diagnostic, comme nous l’expliquerons dans le chapitre suivant, confirmant ainsi des résultats précédemment publiés (Childs et al., 1993). Une récupération de conscience spontanée nous semble peut probable pour expliquer ces 41% de patients diagnostiqués comme étant en état végétatif. En effet, le diagnostic clinique proposé par le corps médical était émis sur base des observations des dernières 24 heures avant l’évaluation réalisée à l’aide de la CRS-R. Une faible expertise dans l’utilisation d’outils standardisés, ainsi qu’une utilisation d’outils peu sensibles pour détecter la conscience nous semble être une explication plus appropriée (Vanhaudenhuyse et al., 2008c). Comme nous le présenterons dans le chapitre suivant, traitant spécifiquement de l’évaluation de la poursuite visuelle, la CRS-R doit sa sensibilité notamment à l’utilisation de matériel spécifique. De plus, l'absence de consensus à propos de certains comportements, tels que le clignement à la menace visuelle, peut également engendrer des problèmes diagnostiques.

Les diagnostics de coma ou d'état végétatif peuvent également être attribués à tort à des patients atteints d'un locked-in syndrome (Bruno et al., 2009). Plusieurs récits témoignent de cette situation, comme le décrit Julia Tavalaro (1997), patiente locked-in considérée par le personnel soignant et médical comme étant un *légume* pendant plus de six ans. Dans ces cas, la difficulté à émettre un diagnostic peut être due à la rareté de ce syndrome, à la difficulté à reconnaître des signes de conscience (Majerus et al., 2005), à une fluctuation de la vigilance typique chez ces patients en stade aigu ou à des déficits cognitifs (Schnakers et al., 2008c) ou sensoriels tels qu'une surdité (Bruno et al., 2009; Keane, 1985; Smart et al., 2008) additionnels au locked-in syndrome. Un mauvais diagnostic peut avoir des conséquences importantes quant à la prise en charge de ces patients (Andrews, 2004).

III. Utilisation d'outils spécifiques pour l'évaluation de la conscience

Comme nous l'avons précédemment expliqué, l'utilisation d'échelles comportementales permet aux cliniciens de statuer sur l'état de conscience des patients non-communiquants. Cependant, l'utilisation de différents stimuli pour tester des aptitudes identiques chez les patients est un des problèmes classiques rencontrés dans la pratique clinique. La poursuite visuelle, un des premiers signes de conscience réapparaissant chez les patients en état de conscience altérée (Giacino et al., 2002), peut être évaluée de différentes manières selon l'échelle clinique employée. Ainsi, la poursuite visuelle est testée à l'aide d'un objet ou d'une personne dans la SMART (Gill-Thwaites and Munday, 2004) ou la WHIM (Shiel et al., 2000), d'un miroir dans la *Western Neuro Sensory Stimulation Profile* (Ansell and Keenan, 1989) ou la CRS-R (Giacino et al., 2004), ou d'un doigt dans la FOUR (Wijdicks et al., 2005). Elle n'est parfois tout simplement pas testée comme c'est le cas dans la GCS (Teasdale and Jennett, 1974) et la GLS (Born, 1988). Selon les critères proposés dans la CRS-R, la poursuite visuelle est considérée comme présente chez un patient si celui-ci démontre un suivi du regard de 45 degrés sans aucune perte de fixation au moins à deux reprises, et ce quelle que soit la direction (Giacino et al., 2004). Le but de notre étude était de déterminer la sensibilité de ces différentes techniques à détecter une poursuite visuelle.

Nous avons étudié la poursuite visuelle chez 51 patients en état de conscience minimale (âge moyen 59±17 ans, 27 d'origine non-traumatique et 24 traumatique), à l'aide d'un miroir, d'un objet et d'une personne se déplaçant dans la chambre du patient

(Vanhaudenhuyse et al., 2008c). Les modalités d'évaluation de la poursuite visuelle étaient celles décrites dans la CRS-R (Giacino et al., 2004). Sur ces 51 patients, 38 présentaient une poursuite visuelle. De ces 38 patients, 36 (95%) démontraient une poursuite visuelle du miroir, alors que 25 (66%) poursuivaient visuellement une personne se déplaçant dans la pièce, et que 21 (55%) suivaient du regard un objet (Figure 3). Les différences entre la poursuite visuelle évaluée à l'aide d'une personne ou d'un objet n'étaient pas significatives, alors qu'elles l'étaient lorsque l'on comparait l'évaluation à l'aide du miroir et des autres stimulations (p>0.01). Par ailleurs, il n'y avait pas de différences significatives entre le type de stimulation employée selon l'étiologie et le temps écoulé après l'accident. De ces 36 patients poursuivant du regard leur reflet dans le miroir, 19 poursuivaient également un objet et une personne, alors que 11 ne présentaient qu'une poursuite visuelle avec le miroir (Tableau 3). Dans le cas de ces 11 derniers patients (29%), la poursuite visuelle du miroir était le seul signe de conscience qu'ils présentaient. Dès lors, si cette poursuite visuelle n'avait pas été détectée grâce à l'utilisation du miroir, ces patients auraient été diagnostiqués comme étant en état végétatif.

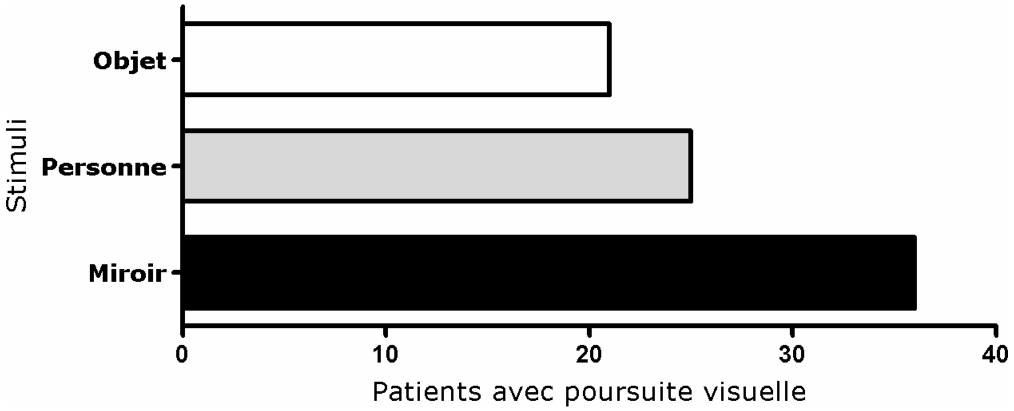


Figure 3 : Représentation graphique du nombre de patients en état de conscience minimale démontrant une poursuite visuelle d'un objet, une personne et un miroir. (Adapté de Vanhaudenhuyse et al., 2008c)

Tableau 3: Nombre de patients en état de conscience minimale avec une poursuite visuelle. (Vanhaudenhuyse et al., 2008c)

Stimuli	Nbre de patients avec une poursuite visuelle n=38 (%)
Miroir uniquement	**11 (29%)**
Personne uniquement	**2 (5%)**
Objet uniquement	**0 (0%)**
Miroir et Personne	**4 (11%)**
Miroir et Objet	**2 (5%)**
Personne et Objet	**0 (0%)**
Miroir, Personne et Objet	**19 (50%)**

Les résultats obtenus dans cette étude démontrent que le type de stimulus employé lors de l'évaluation de la poursuite visuelle était important. L'utilisation de stimuli autoréférentiels (ayant un rapport direct avec la personne elle-même – Neuman and Hill, 1978; Perrin et al., 2006) ou ayant des consonances autoréférentielles/familières (la voix d'un proche – Schiff et al., 2005) étaient plus efficaces pour étudier la conscience ou pour distraire les sujets de leur tâche initiale, et ce aussi bien chez des sujets sains (Brédart et al., 2006; Tong and Nakayama, 1999), que chez des patients sévèrement cérébrolésés (Perrin et al., 2006; Schiff et al., 2005; Schnakers et al., 2008d), autistes (Neuman and Hill, 1978) ou souffrant de la maladie d'Alzheimer (Biringer and Anderson, 1992). Le propre prénom, par exemple, est un stimulus chargé d'une signification personnelle et empreint d'un contenu émotionnel (Laureys et al., 2007). En 1953, Cherry propose le concept de phénomène *cocktail party* pour décrire cette faculté du propre prénom à attirer l'attention des individus. Plusieurs études ont ensuite démontré que le propre prénom était mieux détecté que d'autres mots (Wolford and Morrison, 1980) et qu'il influençait les performances des sujets lors de tâches attentionnelles (Moray, 1959; Wood and Cowan, 1995). Cependant, certains travaux nuancent ces affirmations et suggèrent que le propre prénom facilite l'identification, mais ne joue pas toujours un rôle de distracteur attentionnel (Bundesen et al., 1997). Parallèlement au propre prénom, le propre visage a également fait l'objet de plusieurs travaux depuis les années 1970. La reconnaissance de soi chez l'animal et l'humain est testée par un paradigme au cours duquel les individus voient leur visage marqué d'une tâche dans un miroir (dont l'individu n'a pas conscience). Ces premières études ont mis en évidence que la conscience de soi était le propre de l'homme, ainsi que de certains primates (Gallup, 1970, 1979). D'autres études, plus récentes, ont mis en évidence le même type de résultats chez des éléphants (Plotnik et al., 2006) et des dauphins (Reiss and Marino, 2001). Par ailleurs, cette capacité à reconnaître son reflet dans un miroir a apparaît chez les bébés dès l'âge de 18 à 24 mois (Anderson, 1984; Mans et al., 1978; Nielsen et al., 2006), voir plus tôt encore (Rochat and Striano, 2002). Le propre visage aurait également une capacité à attirer l'attention des individus (Brédart et al., 2006; Tong and Nakayama, 1999). Récemment, des études ont proposé que l'effet du propre visage soit davantage une difficulté du sujet à désengager son attention du stimulus, plutôt qu'un effet prioritaire du propre visage sur tout autre stimulus (Devue et al., 2009). De plus, l'effet attentionnel de ces stimuli autoréférentiels n'est observé que lorsque les propres prénoms ou visages sont présentés dans le champ visuel attentionnel des sujets (Devue and Brédart, 2008; Gronau et al., 2003).

Pourquoi ce type de stimulation est-il utilisé dans les échelles d'évaluation de la conscience ? Notons, tout d'abord, que le miroir n'est pas seulement utilisé pour l'évaluation de la conscience des patients cérébrolésés. En effet, chez certains patients souffrant de la maladie d'Alzheimer, l'utilisation du miroir a été démontrée comme plus puissante que d'autres stimulations, telles qu'un enregistrement vidéo, pour évaluer la conscience de soi résiduelle (Biringer and Anderson, 1992). Le même type d'observation a pu être réalisé chez des enfants autistes (Neuman and Hill, 1978). De plus, certaines études ont démontré que les réponses comportementales, mais également neuronales à des stimuli directement liés à la conscience de soi (propre prénom) sont parmi les premières à réapparaître chez ces patients qui par la suite récupèrent d'autres signes de conscience (Di et al., 2007; Laureys et al., 2004b). Cependant, le fait de présenter un comportement mieux adapté lors de la présentation de son reflet dans un miroir par rapport à un objet quelconque implique-t-il réellement un processus de reconnaissance de soi ? Le test du miroir peut échouer pour de nombreuses raisons autres qu'un trouble de la reconnaissance de soi. Par exemple, la reconnaissance de son reflet dans un miroir implique une compréhension de la relation existante entre l'environnement réel et l'environnement reflété dans le miroir (Breen et al., 2001; Priel and de Schonen, 1986). Ce postulat pourrait expliquer pourquoi certains patients (5%) n'étaient pas capables de suivre un miroir du regard alors qu'ils pouvaient suivre un objet ou une personne se déplaçant dans la pièce.

Certains expliquent ce phénomène de puissance des stimuli autoréférentiels par le fait que les processus de traitement des informations liées à la conscience de soi sont complètement distincts des processus de traitement de toute autre information (pour une revue, voir Gillihan and Farah, 2005). Par ailleurs, les études en neuroimagerie démontrent principalement une implication des cortex préfrontal, frontal, cingulaire antérieur et précunéus; mais également de la jonction temporo-pariétale, avec une latéralité dominante à droite, dans le processus de reconnaissance du propre visage comparé à d'autres visages (Kircher et al., 2000; 2001; Morita et al., 2008; Platek et al., 2006; Sugiura et al., 2005; Uddin et al., 2005). Ces régions sont connues comme étant les plus atteintes chez les patients en état végétatif qui, eux, ne présentent aucune poursuite visuelle, même de leur reflet dans un miroir (Laureys et al., 2004a). En conclusion, les implications cliniques de cette étude ne sont pas négligeables. Grâce à l'utilisation du miroir dans la détection d'une poursuite visuelle, nous avons pu éviter que plus d'un cinquième des patients impliqués dans ce travail soient mal diagnostiqués. En effet, ces patients démontraient uniquement une poursuite visuelle du miroir comme comportement conscient.

IV. Comportements ambigus de conscience

Dans le but d’améliorer les évaluations comportementales de conscience, nous avons étudié la signification du clignement à la menace visuelle chez des patients en état végétatif (Vanhaudenhuyse et al., 2008a). 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. Le réflexe de clignement, que ce soit en réponse à un son, à une stimulation lumineuse, ou à une menace visuelle implique que les processus sensoriels soient intacts au niveau du tronc cérébral, mais ne veut pas nécessairement signifier que ces mécanismes soient préservés au niveau du cortex (Posner et al., 2007). En effet, des patients souffrant d’une destruction complète du cortex visuel peuvent présenter un réflexe de clignement à une stimulation lumineuse (Hackley and Johnson, 1996), mais pas à une menace visuelle (Liu and Ronthal, 1992). Actuellement, il n’existe pas de consensus sur le lien entre la présence de ce comportement et la présence résiduelle d’une conscience. Pour certains auteurs, le clignement à la menace visuelle est un comportement considéré comme cognitif qui traduit une conscience (Liu and Ronthal, 1992; Wade and Johnston, 1999). Le groupe *Multi-Society Task Force on PVS* (1994) insiste sur la prudence à avoir lors du diagnostic d’état végétatif en présence d’un tel comportement. Selon les guidelines australiens et londoniens, une réponse à une menace visuelle est habituellement absente chez les patients en état végétatif (Australian Government National Health and Medical Research Council, 2003; Royal College of Physicians, 2003). Jennet (2002), quant à lui, souligne que la présence d’un clignement à la menace visuelle n’est pas une preuve en soi de l’existence d’une conscience. Enfin, la signification dans l’évaluation de la conscience de ce comportement n’est pas discutée dans certains guidelines, comme c’est le cas par exemple pour l’*Aspen Neurobehavioral Workgroup* (Giacino et al., 2002).

Nous avons démontré que le réflexe de clignement à la menace visuelle, testé tel que décrit par Giacino et al. (2004), était compatible avec le diagnostic d’état végétatif (Vanhaudenhuyse et al., 2008a). Sur 91 patients en état végétatif (âge 45±20 ans, 41 d’origine traumatique, 50 non-traumatique), 46 patients (51%) démontraient un réflexe de clignement à la menace. Par ailleurs, sur ces 46 patients, 10 sont décédés, 22 sont restés en état végétatif et

14 ont émergé de leur état végétatif. Quant aux 45 patients (49%) ne démontrant pas de réflexe de clignement à la menace visuelle, 8 sont décédés, 28 sont restés en état végétatif et 9 ont récupéré un certain degré de conscience. Le taux de récupération n'était dès lors pas significativement différent chez les patients présentant et ne présentant pas de réflexe de clignement à la menace visuelle (Tableau 4). Enfin, ces données nous ont permis de conclure que la valeur prédictive positive du réflexe de clignement à la menace visuelle était de 30%, tandis que la valeur prédictive négative était de 80%.

Tableau 4: Patients en état végétatif (EV) avec et sans réflexe de clignement à la menace visuelle. REC : patients ayant récupéré de leur état végétatif, TBI : traumatique, NTBI : non-traumatique, DCD : décédé (Vanhaudenhuyse et al., 2008a)

EV avec réflexe de clignement à la menace (n=46)			**EV sans réflexe de clignement à la menace (n=45)**		
REC	**EV**	**DCD**	**REC**	**EV**	**DCD**
14 (5 NTBI)	22 (14 NTBI)	10 (7 NTBI)	9 (2 NTBI)	28 (17 NTBI)	8 (5 NTBI)

Par cette étude, nous avons mis en évidence que le réflexe de clignement à la menace visuelle était compatible avec un diagnostic d'inconscience – d'état végétatif, contrairement aux clignements spontanés des yeux qui sont reportés comme étant directement liés à des processus cognitifs. Ces derniers sont influencés par différents facteurs tels que le niveau de vigilance (Barbato et al., 2000), des processus cognitifs de base (processus attentionnels – Tsubota et al., 1999, de reconnaissance – Fukuda, 1994; Viggiano and Mecacci, 2000, ou de mémorisation – Olichney et al., 1993; Viggiano and Mecacci, 2000) ou des processus cognitifs plus complexes (mécanismes de concentration – Yamada, 1998, et de lecture – Bentivoglio et al., 1997; Orchard and Stern, 1991). Nos résultats ne corroborent pas les études postulant qu'une réponse à une menace visuelle implique nécessairement une conscience de cette menace (Wade and Johnston, 1999; Jennett et al., 1997). Certains expliquent également le réflexe de clignement à la menace par des causes émotionnelles et nerveuses propres au sujet (Hall, 1945). Ces conclusions coïncident avec les résultats des études neuro-ophtalmologiques réalisées chez des patients atteints de cécité corticale, de syndrome de négligence ou de syndrome de Balint. Ces études cliniques proposent que la présence d'un clignement à la menace visuelle requière une préservation du cortex visuel primaire, ainsi que des mécanismes de plus haut niveau impliqués dans les processus d'attention visuelle, localisés dans les lobes pariétaux inférieurs et frontaux (Liu and Ronthal, 1992). Déjà en 1934, Rademaker et Garcin expliquaient que le réflexe de clignement à la menace pouvait être supprimé par des lésions corticales, rolandiques et occipito-rolandiques et proposaient donc que ce comportement soit classé dans les réflexes visuels tels que le réflexe cornéen (Rademaker and Garcin, 1934). Nos résultats confirment ces derniers postulats et démontrent, en outre, que la présence ou l'absence de ce comportement ne peut prédire d'une bonne ou mauvaise récupération de la conscience chez des patients en état végétatif.

V. Conclusion

Même si beaucoup de progrès ont été faits depuis la première description de l'état végétatif proposée par Jennet et Plum (1972), la description des états de conscience altérée est toujours limitée à des catégories générales (telles que l'état végétatif et l'état de conscience minimale) établies sur base de corrélations entre les observations cliniques et les études en neuroimagerie (Fins, 2009). Ces catégories limitent les cliniciens à donner une *étiquette* diagnostique globale ne permettant pas de différencier les patients au sein d'une même catégorie. En effet, quelle que soit la complexité de leurs comportements conscients (poursuite visuelle, réponses à la commande ou une communication non fonctionnelle), les patients sont diagnostiqués comme étant en état de conscience minimale (Giacino et al., 2002). Il nous semble important d'approfondir ces descriptions diagnostiques afin de pouvoir caractériser au mieux les patients. Une première étape est de définir clairement ce que nous considérons comme un signe de conscience. L'absence de consensus quant à l'expression d'une conscience, telle qu'observée pour le clignement à la menace visuelle (Vanhaudenhuyse et al., 2008a), n'aide pas le clinicien à émettre un diagnostic précis. L'utilisation d'outils appropriés est également importante. En effet, différencier un comportement réflexe d'un comportement volontaire est souvent difficile. Si ces derniers ne sont pas étudiés avec des techniques sensibles, comme un miroir pour tester la poursuite visuelle (Vanhaudenhuyse et al., 2008c), le clinicien pourrait omettre la présence de signes de conscience.

Enfin, si les évaluations comportementales doivent encore être affinées (Childs et al., 1993; Andrews et al., 1996; Schnakers, Vanhaudenhuyse et al., 2009b), les techniques de traitement validées sont encore très peu développées. Certains traitements peuvent être proposés afin d'améliorer le confort des patients, comme par exemple des injections de Baclofen (agoniste des récepteurs GABA) qui diminueront la spasticité et donc les douleurs liées à ces contractions musculaires conduisant parfois à des fractures spontanées (Taira, 2009). D'autres traitements pharmacologiques ont été testés chez des patients en état végétatif et en état de conscience minimale, mais les résultats qui en ressortent sont jusqu'à présent peu satisfaisants. L’Amantadine (agent dopaminergique) a été mise en lien avec une évolution comportementale favorable de patients dont l’étiologie était traumatique (Sawyer et al., 2008; Whyte et al., 2005). Une augmentation de l’activité cérébrale fronto-pariétale a pu être mise en évidence chez un patient en état de conscience minimale après l’administration de l’Amantadine (Schnakers et al., 2008a). D’autres molécules comme le Levodopa ou la Bromocriptine (agents dopaminergiques – Passler and Riggs, 2001), le Baclofen (Taira, 2009) et le Zolpidem (somnifère – Clauss and Nel, 2006; Whyte and Myers, 2009) ont également été mises en relation avec une meilleure récupération des patients en état de conscience altérée. Malheureusement, l’ensemble de ces études est réalisé sur de petits groupes de patients ou sans contrôle placebo et ne permet donc pas de généraliser les résultats obtenus (Demertzi, Vanhaudenhuyse et al., 2008). Quant aux traitements non pharmacologiques, diverses méthodes sont proposées. La stimulation intracrânienne peut provoquer un certain éveil chez des patients en état végétatif (Yamamoto and Katayama, 2005), mais son efficacité semble assez limitée. Récemment, le groupe du Pr. Schiff a proposé un protocole de stimulation intracrânienne se basant sur les performances comportementales et le type de lésion cérébrale des patients (Schiff and Fins, 2007). En appliquant une stimulation au niveau du thalamus chez un patient en état de conscience minimale chronique d’origine traumatique, ils sont parvenus à améliorer les réponses d’éveil, motrices et d’interactions avec l’environnement de ce patient (Schiff et al., 2007). A nouveau, ce protocole doit être validé sur une population plus importante de patients afin d’objectiver ce que nous pouvons réellement attendre de ce type de traitement invasif. Les programmes de stimulations sensorielles et de kinésithérapie sont, quant à eux, utilisés afin de prévenir toute complication physique, mais n’ont encore jamais été démontrés comme étant significativement efficaces (Lombardi et al., 2002). Enfin, des outils objectivant le vécu douloureux de ces patients incapables de communiquer leur ressenti sont proposés. Plusieurs échelles d’évaluation de la douleur ont été développées pour des populations telles que les nouveaux-nés ou les patients souffrant de démences liées au vieillissement (pour une revue, voir Schnakers and Zasler, 2007). Ce n’est que récemment qu’une échelle d’évaluation de la douleur a été proposée spécifiquement pour les patients en état de conscience altérée. La *Nociception Coma Scale* (Schnakers et al., 2010) a été validée pour évaluer la perception douloureuse des patients en état végétatif et en état de conscience minimale. Par l’observation de comportements contingents à des stimulations nociceptives, qu’ils soient moteurs (localisations, flexions, réponses stéréotypées), verbaux (verbalisations, vocalisations, grognements), visuels (fixation, sursaut), ou faciaux (pleurs, grimaces, sursaut), la *Nociception Coma Scale* permet de déterminer si la douleur chez le patient est sévère, modérée, légère ou absente. Nous pensons que cette échelle peut se révéler utile pour la prise en charge à court et à long terme, puisqu'elle permet aux cliniciens d'objectiver la perception douloureuse de ces patients et leur offre ainsi la possibilité d'adapter le titrage morphinique à administrer.

Aujourd'hui, la position des médecins face aux patients en état de conscience altérée est encore difficile. La pratique médicale repose sur des principes moraux et éthiques tels que l'autonomie du patient, la bienveillance et la justice (Beauchamp and Childress, 2001). Confrontés à des patients incapables d'exprimer leurs désirs, les médecins se retrouvent face à des dilemmes devant lesquels ils doivent faire des choix à la place du patient, parfois sans savoir exactement quel pronostic ils peuvent espérer (Young, 2009). Les cliniciens devraient pouvoir se baser sur le pronostic du patient, obtenu grâce à l'ensemble de résultats d'examens (Fins, 2007; Young, 2009). Aujourd'hui, des marqueurs pronostiques sont à notre disposition pour les patients dont l'étiologie est anoxique (Boveroux et al., 2008; Wijdicks et al., 2006), mais très peu de données existent pour les patients dont l'étiologie est traumatique. Dès lors, comment demander à des médecins de prendre des décisions si nous ne pouvons leur offrir qu'une information objective limitée par rapport à la récupération des patients post-coma ? Comment répondre aux familles chargées d'interrogations quant à l'avenir de leur proche, alors que nous n'avons encore que très peu de réponses sur le pronostic de ces patients ? De plus, au-delà des aspects médicaux, les états végétatif et de conscience minimale chroniques sont à l'origine d'autres interrogations, qu'elles soient d'ordre économique, légale, morale ou religieuse. Cela souligne l'intérêt d'une recherche translationnelle proposant des modèles diagnostiques et pronostiques sensibles et fiables.

MARQUEURS PARACLINIQUES ELECTROPHYSIOLOGIQUES DE LA CONSCIENCE

Sur base de l'article suivant :

Cognitive event-related potentials in comatose and post-comatose states.
Vanhaudenhuyse A., Laureys S., Perrin F.
Neurocritical Care 2008: 8, 262-270

Détecter un comportement volontaire et le différencier d'un comportement réflexe reste difficile (Schnakers, Vanhaudenhuyse et al., 2009b; 2008c). La nécessité d'outils para-cliniques et de marqueurs objectifs de la conscience n'est plus à démontrer. Les instruments électrophysiologiques sont un des moyens de pallier au manque de sensibilité de l'évaluation comportementale (Vanhaudenhuyse et al., 2008b). Ces techniques nous permettent d'obtenir des informations quant aux capacités cognitives des patients, indépendamment de leurs capacités motrices qui sont souvent sources de mauvaise interprétation. Les potentiels évoqués sont à notre disposition afin de compléter l'évaluation comportementale des patients en état de conscience altérée. Cette méthode est dérivée de l'électroencéphalographie (EEG). L'EEG est une technique qui consiste à enregistrer l'activité électrique cérébrale, permettant d'explorer des états physiologiques ou pathophysiologiques (par exemple, identifier le niveau d'éveil ou l'épilepsie). Si l'on veut détecter des changements plus subtils dans l'activité électrique cérébrale, tel qu'une réponse spécifique à un stimulus donné, des calculs de moyenne du signal sont nécessaires. Cette technique de moyenne, également appelée calcul de potentiels évoqués, met en évidence une déflexion (ou une composante) de l'activité électrique cérébrale liée à l'activation successive de structures nerveuses impliquées dans les processus de traitement d'informations motrices, sensorielles ou cognitives. Les potentiels évoqués peuvent être de type *exogènes* ou *endogènes*. Les potentiels évoqués dits exogènes, ou de courte latence (entre 0 et 100ms), correspondent à l'activation des processus du cortex primaire. Tandis que les potentiels évoqués endogènes, ou cognitifs (apparaissant après 100ms), sont le reflet d'une activité corticale ou sous-corticale, incluant les aires associatives. Alors que les potentiels évoqués de courte latence sont influencés par les propriétés physiques du stimulus, les potentiels évoqués cognitifs dépendent de la signification du stimulus, des conditions expérimentales et des niveaux d'attention et d'éveil. Les potentiels évoqués sont utilisés à titre prédictif de la récupération de conscience des patients en coma dans les unités de soins intensifs.

Dans ce travail, des valeurs prédictives seront calculées en fonction de la relation existant entre la présence ou l'absence de potentiel et le degré de récupération des patients. Différentes valeurs de prédiction et de sensitivité peuvent être calculées : (1) la *valeur prédictive positive pour un degré de récupération favorable – PV+* – correspond au nombre de patients avec une récupération favorable et une composante / nombre total de patients avec cette composante ; (2) la *valeur prédictive positive pour un mauvais degré de récupération – PV-* – correspond au nombre de patients ayant une mauvaise récupération et une absence de composante / nombre total de patients sans composante ; (3) la *valeur de spécificité pour une* *récupération favorable – Sp+ –* correspond au nombre de patients ayant une mauvaise récupération et aucune composante / nombre de patients avec une mauvaise récupération ; (4) la *valeur de spécificité pour une mauvaise récupération – Sp- –* correspond au nombre de patients ayant une récupération favorable et une composante / nombre de patients ayant une récupération favorable. Nous calculerons, ci-après, ces degrés de prédiction et de sensitivité, particulièrement pour les potentiels évoqués cognitifs qui ne sont pas encore unanimement reconnus comme ayant une valeur fiable de prédiction de récupération d'un coma.

De plus, nous verrons que si les potentiels évoqués de courte latence sont utiles pour prédire un mauvais pronostic, ils le sont moins pour prédire un pronostic favorable et moins encore pour évaluer les fonctions cognitives résiduelles. Le but de ce travail était également de passer en revue les études existantes de 1980 à 2007 (les données ont été adaptées afin de considérer les récentes publications) sur les potentiels évoqués cognitifs étudiés chez des patients en coma, en état végétatif ou en état de conscience minimale mis en lien avec leur degré de récupération.

I. Potentiels évoqués de courte latence

Aujourd'hui, la valeur prédictive des potentiels évoqués de courte latence est bien connue (Laureys et al., 2005b). L'ensemble des études démontre que le taux de faux négatifs est presque inexistant, c'est-à-dire que la majorité des patients ne présentant pas de potentiel évoqué de courte latence bilatéralement ont peu de chance de récupérer une conscience. Le taux de faux positifs est, quant à lui, élevé, signifiant donc que des potentiels de courte latence peuvent être détectés chez des patients ayant un pronostic clinique mauvais. Une absence bilatérale des potentiels évoqués somatosensoriels (PES), reflétant l'absence d'activation des processus somatosensoriels sous-corticaux et du cortex somatosensoriel primaire, est associée à un pronostic de mort cérébrale ou d'état végétatif, et cela aussi bien chez des patients adultes (PV- 100% - Cant et al., 1986; Lew et al., 2003; Logi et al., 2003; Robinson et al., 2003; Young, 2009), que chez des enfants (Carter and Butt, 2005; Suppiej et al., 2009). De plus, les patients qui récupèrent une certaine conscience démontrent une présence de PES normaux (Sp- 100%). Cependant, comme diverses études l'ont mis en évidence, des PES normaux ont également été associés à un nombre important de faux positifs (Amantini et al., 2005; Cant et al., 1986; Carter and Butt, 2001; De Giorgio et al., 1993), suggérant que les PES n'étaient pas un facteur fiable de bonne récupération. Enfin, le délai d'évaluation des PES semble également avoir son importance. Une évaluation réalisée le troisième jour après l’accident est rapportée comme étant plus fiable (quant à sa valeur pronostique) qu’une évaluation des PES faite dans un délai plus court (Houlden et al., 2010). Quant à l’absence de potentiels évoqués auditifs (*brainstem auditory-evoked potentials – BAEPs*), elle est considérée comme prédictive d’un mauvais pronostic. A l’inverse, leur présence n’indique pas de manière fiable un bon pronostic (Cant et al., 1986; Fischer et al., 1988; 2001; Garcia-Larrea et al., 1992; Guerit et al., 1993). De même, l’absence des potentiels évoqués auditifs de latence moyenne (*middle-latency auditory-evoked potentials – MLAEPs*), traduisant une activation thalamique et des cortex auditifs primaires, est spécifiquement associée à un mauvais pronostic chez les patients dont l’étiologie est anoxique (Fischer et al., 2006; Fischer et al., 2001; Litscher et al., 1995).

II. Potentiels évoqués cognitifs

La composante N100

L’onde appelée N100 traduit une déflexion négative du signal, apparaissant aux alentours de 100ms, en réponse à un stimulus auditif (Hillyard et al., 1973). Elle correspond à l’activation des cortex auditifs et peut également être associée à une activation des aires préfrontales dorso-latérales (Liegeois-Chauvel et al., 1994; Naatanen and Picton, 1987; Scherg and Von Cramon, 1985). La présence d’une onde N100 chez des patients en état de conscience altérée suggère que les cortex auditifs primaires sont fonctionnellement préservés. Certains postulent que sa présence prédit une récupération de la conscience (Fischer et al., 2004; 2001; Mazzini et al., 2001 – Tableau 5), alors que d’autres démontrent le contraire (Glass et al., 1998; Guerit et al., 1999; Mutschler et al., 1996). De plus, deux études proposent que l’absence de l’onde N100 soit considérée comme prédictive de mauvaise récupération (Glass et al., 1998; Mutschler et al., 1996).

La composante de négativité de discordance ou MMN

L’onde MMN est une composante négative apparaissant après 100 à 200ms suite à un changement inattendu dans une suite de stimuli auditifs monotones chez des sujets inattentifs à ces stimulations (Naatanen et al., 1978; 1997). Cette onde traduit une activation des cortex auditifs primaires et frontaux (Alho, 1995; Celsis et al., 1999) et permet d’évaluer l’intégrité des processus de mémoire échoïque. Peu d’études se sont penchées sur la valeur pronostique de la MMN chez des patients en état de conscience altérée (Tableau 5), mais celles réalisées démontrent que cette onde semble être prédictrice d’une récupération particulièrement chez les patients dont l'étiologie est anoxique (Kane et al., 1993; 1996; Suppiej et al., 2009). De plus, une étude rétrospective réalisée sur 346 patients rapporte une valeur pronostique de récupération de la MMN chez les patients, toutes étiologies confondues (Fischer et al., 2004). La majorité des patients qui n'ont pas récupéré ne présentaient pas de MMN (Fisher et al., 2006; 2004; 2001; Naccache et al., 2005). Ces derniers résultats ont été plus récemment confirmés par Naccache et al. (2005). Dans leurs études, Kotchoubey et al. (2003 ; 2005) ont mis en évidence une MMN chez 65% des patients en état végétatif et 34% des patients en état de conscience minimale. Les auteurs ont démontré que des sons complexes (sons périodiques, non sinusoïdaux) étaient plus puissants pour provoquer une MMN que des sons purs (sons sinusoïdaux). Une dernière étude a permis de démontrer que l'amplitude de la MMN augmentait lorsque des patients en état végétatif récupéraient un état de conscience minimale (Wijnen et al., 2007).

La composante P300

L'onde P300 est une composante positive apparaissant 300ms après la présentation d'un stimulus rare dans une série de stimuli identiques (Sutton et al., 1965). L'amplitude de cette onde est modulée par la probabilité d'apparition de ce stimulus rare (Picton, 1992). L'onde P300 peut être catégorisée en deux *sous-ondes*: la P3a, apparaissant après 250ms, de topographie plutôt frontale et sensible à une détection involontaire d'un stimulus ; la P3b, apparaissant après 350ms, de topographie plutôt pariétale et principalement modulée par une discrimination attentionnelle (Squires et al., 1975). L'onde P3b apparaît également lorsque le stimulus déviant a une signification particulière pour le sujet, comme le propre prénom par exemple (Berlad and Pratt, 1995; Perrin et al., 1999). L'onde P300 peut être considérée comme reflétant l'instant auquel le sujet a détecté le stimulus déviant (Verleger, 1988) et proviendrait d'une activation temporale médiale et latérale, thalamique, pariétale et préfrontale (Baudena et al., 1995; Halgren et al., 1995; Smith et al., 1986).

Dans la plupart des études, la présence d'une onde P300 chez un patient est corrélée avec une récupération de la conscience, tandis que son absence traduit un mauvais pronostic (Tableau 5). Cependant, les données sont encore hétérogènes et comme pour la MMN, certaines études démontrent qu'une proportion importante des patients présentant une P300 récupèrent (De Giorgio et al., 1993; Gott et al., 1991; Guerit et al., 1999; Yingling et al., 1990), tandis que d'autres affirment le contraire (Harris and Hall, 1990; Mutschler et al., 1996). Ces résultats discordants peuvent être expliqués par le nombre de patients inclus dans les études, ainsi que par le petit nombre de patients qui démontrent une P300. L'utilisation de stimuli émotionnels augmente la probabilité que des patients post-coma démontrent une P300. En comparant deux paradigmes *oddball* – avec et sans stimulus émotionnel (voix d'un proche ou le propre prénom du patient) – une onde P300 a pu être obtenue dans 36 à 38% des patients lorsqu'il n'y avait aucune valence émotionnelle, et dans 52 à 56% des patients lorsque les stimuli avaient une valence émotionnelle (Signorino et al., 1995; 1997b). Dans ces études, la majorité des patients ayant présenté une P300 ont récupéré un certain degré de conscience. Ces résultats ont été confirmés par Lew et al. (2003; 1999) qui ont mis en évidence une onde P300 de plus large amplitude en réponse au mot *maman*, en comparaison à un son sans signification particulière. D'autres données, obtenues sur un petit groupe de patients, tendent à la même conclusion à savoir que la présence d'un P300, même en réponse à un son neutre, peut être considérée comme un facteur de bon pronostic (Glass et al., 1998; Rappaport et al., 1991). Plus récemment, une étude réalisée sur 34 patients d'étiologie traumatique a démontré que 88% des patients présentant une onde P300 émergeaient de l'état végétatif dans les 3 à 6 mois après l'accident, alors qu'aucune récupération n'avait pu être observée chez les patients n'ayant pas présenté de P300 (Cavinato et al., 2009). Enfin, certains auteurs suggèrent qu'une onde P300 a plus de chance d'apparaître chez des patients en état végétatif ou en état de conscience minimale, en réponse à un son complexe, comparé à un son pur (respectivement 22% *vs* 15% chez les patients en état végétatif, et 31% *vs* 8% chez les patients en état de conscience minimale) (Kotchoubey and Lang, 2001; Kotchoubey et al., 2002). Le nombre de patients présentant une onde P300 est plus important si un stimulus émotionnel tel que le propre prénom du patient est utilisé (Giorgianni et al., 1997; Marosi et al., 1993; Mazzini et al., 2001; Prevec et al., 1993). Perrin et al. (2006) ont mis en évidence une onde P300 en réponse au propre prénom chez des patients en état végétatif et en état de conscience minimale (Figure 4). L'ensemble de ces résultats suggère que les patients en état végétatif et en état de conscience minimale aient des processus de traitement de l'information verbale partiellement préservés, notamment par leur capacité à détecter des stimuli tels que leur propre prénom. La présence d'une onde P300 semble pouvoir être un indicateur de bon pronostic, mais des études sur des échantillons plus importants sont encore nécessaires pour confirmer ces conclusions.

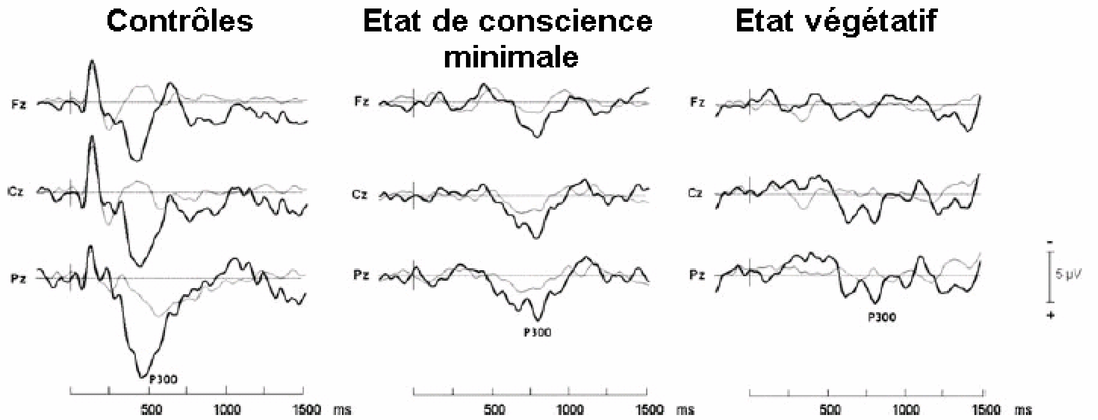


Figure 4 : Potentiels évoqués cognitifs en réponse au propre prénom (ligne noire), ainsi qu'à d'autres prénoms (ligne grise), enregistrés chez des sujets contrôles, des patients en état de conscience minimale et en état végétatif. (Adapté de Vanhaudenhuyse et al., 2008b)

La composante N400

L'onde N400 est une composante négative apparaissant 400ms après la présentation du stimulus, influencée par une discordance phonologique ou sémantique du stimulus par rapport au contexte dans lequel il est apparu, même si le sujet ne dirige pas directement son attention sur la stimulation (Connolly et al., 1990; Kutas and Hillyard, 1989; 1980; Perrin et al., 2003). L'onde N400 provient d'une activité des cortex temporaux latéraux et médiaux, ainsi que frontal et pariétal gauches (Hagoort et al., 1996; McCarthy et al., 1995; Smith et al., 1986).

Peu d'études ont été réalisées sur la composante N400 chez les patients en état de conscience altérée. Schoenle et Witzke (2004) ont mis en évidence la présence d'une onde N400 en réponse à des mots sémantiquement incongrus chez certains patients en état végétatif (12%), ainsi que chez 77% des patients qu'ils dénommaient *near-vegetative state* (patients présentant une poursuite ou une fixation visuelle ou des réponses orientées – état de conscience minimale), et chez 90% des patients démontrant des *comportements appropriés – meaningful behavior* (patients présentant un comportement tel qu'une réponse à la commande). Ces résultats suggèrent donc que la majorité des patients en état de conscience minimale, mais également certains patients en état végétatif, ont des processus sémantiques relativement préservés. Malheureusement, aucune donnée pronostique n'existe encore pour l'onde N400.

Tableau 5: Valeur prédictive positive pour un degré de récupération favorable (PV+) et pour un mauvais degré de récupération (PV-) ; valeur de spécificité pour une récupération favorable (Sp+) et pour une mauvaise récupération (Sp-). Les valeurs en gras sont supérieures à 80%. (Vanhaudenhuyse et al., 2008b)

	1er Auteur (année)	Nombre de patients	PV+ % (95%, IC)	PV- % (95%, IC)	Sp+ % (95%, IC)	Sp- % (95%, IC)
N100	Mutschler (1996)	20	40 (12-73)	**100** (69-100)	63 (35-85)	**100** (40-100)
	Glass (1998)	8	29 (4-71)	**100** (2-100)	17 (0-64)	**100** (16-100)
	Guérit (1999)	103	77 (66-87)	54 (43-65)	56 (45-67)	76 (65-85)
	Mazzini (2001)	21	**83** (58-95)	41 (22-66)	**83** (58-95)	41 (22-66)
	Fischer (2004)	346	**80** (74-86)	48 (40-56)	65 (55-73)	67 (61-73)
MMN	Kane (1996)	54	**100** (86-100)	45 (27-64)	**100** (77-100)	56 (40-72)
	Fischer (2004)	346	**89** (80-94)	38 (32-44)	**91** (83-95)	33 (27-39)
	Suppiej (2009)	1 (enfant)	-	-	-	-
P300	Yingling (1990)	8	**100** (16-100)	75 (35-97)	**100** (54-100)	50 (7-93)
	Gott (1991)	20	**83** (36-99)	71 (42-92)	**91** (59-99)	56 (21-86)
	Rappaport (1991)	8	**88** (47-99)	**100** (2-100)	50 (1-99)	**100** (54-100)
	DeGiorgio (1993)	20	**83** (36-99)	71 (42-92)	**91** (59-99)	56 (21-86)
	Mutschler (1996)	20	50 (12-88)	**93** (66-99)	81 (54-96)	75 (19-99)
	Guérit (1999)	103	**100** (96-100)	41 (30-52)	**100** (96-100)	18 (10-28)
	Signorino (1997)	25	**87** (60-98)	50 (19-81)	71 (29-96)	72 (47-90)
	Glass (1998)	8	33 (4-78)	**100** (16-100)	33 (4-77)	**100** (16-100)
	Mazzini (2001)	21	58 (34-78)	0 (0-16)	**83 (**58-95)	0 (0-16)
	Lew (2003)	22	71 (29-96)	**87** (59-98)	**87** (60-98)	71 (29-96)
	Cavinato (2009)	34	**100** (85-100)	**100** (63-100)	**100** (63-100)	**88** (70-97)

III. Conclusion

Nous avons mis en évidence l’intérêt des potentiels évoqués de courte latence comme marqueur d’un mauvais pronostic et des potentiels évoqués cognitifs comme prédictifs d’une récupération de la conscience. Nous avons également vu que les potentiels évoqués cognitifs pouvaient être utiles lors de l’évaluation des fonctions cognitives résiduelles de ces patients. Ils permettent d’évaluer l’intégrité des processus de mémoire échoïque (MMN), de discrimination acoustique et sémantique (P300), ou de détection d’incongruités langagières (N400). L’hétérogénéité des résultats obtenus peut être en partie expliquée par différents facteurs tels que les différentes techniques d’acquisition utilisées, les différents niveaux de conscience des patients inclus, le petit nombre ainsi que les étiologies variables des patients. Avant de pouvoir tirer des conclusions fiables quant à la valeur pronostique des potentiels évoqués cognitifs, il faudrait étudier des populations plus larges de patients, en différenciant clairement les résultats obtenus chez des patients donc l'accident est d'origine traumatique de ceux obtenus chez des patients d'étiologie non-traumatique. De plus, le degré de récupération des patients devrait être étudié avec d'autres outils que la GOS permettant de quantifier la récupération. En effet, cela permettrait de différencier les patients ayant récupéré un état de conscience minimale de ceux ayant récupéré un niveau de conscience normale. Les fonctions cognitives pourraient également être évaluées de manières plus approfondies.

D'un point de vue diagnostique, ces résultats ne permettent pas de différencier un patient conscient d'un patient inconscient. En effet, les potentiels évoqués cognitifs nous permettent d'évaluer l'état des processus de traitement de l'information mais ne peuvent cependant pas nous donner d'information sur ce qui relève du traitement volontaire ou automatique. Dans ce cadre, un nouveau paradigme dit *actif* a été développé dans lequel il était demandé aux participants de compter activement le nombre de fois qu'ils entendaient leur prénom ou un autre prénom, alors que simultanément des enregistrements de potentiels évoqués étaient réalisés (Schnakers et al., 2009a; 2008d). Les résultats, qu'ils soient individuels ou obtenus sur le groupe, ont démontré une plus grande amplitude de la P300 en réponse au propre prénom, lorsque les patients en état de conscience minimale devaient réaliser la tâche active (compter leur prénom) en comparaison avec une écoute passive. Cette onde P300 était comparable à celle observée chez des sujets contrôles, alors qu'aucun changement n'a pu être détecté chez les patients en état végétatif (Schnakers et al., 2008d). De plus, ce même paradigme a également permis de détecter la présence d'un état de conscience tout à fait préservé chez une patiente en locked-in syndrome complet (Schnakers et al., 2009a). Cette nouvelle technique de potentiels évoqués actifs se révèle d'une grande utilité afin d'évaluer l'état de conscience de patients présentant souvent des déficits moteurs sévères.

NEUROIMAGERIE ET ETATS DE CONSCIENCE ALTEREE

Sur base des articles suivants :

Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients.
Vanhaudenhuyse A.*, Noirhomme Q.*, Tshibanda L., Bruno MA., Boveroux P., Schnakers C., Soddu A., Perlbarg V., Ledoux D., Brichant JF., Moonen G., Maquet P., Greicius MD., Laureys S., Boly, M. *Co-first author
Brain 2010: 133, 161-171

Two distinct neuronal networks mediate the awareness of environment and of self.
Vanhaudenhuyse A.* , Demertzi, A.*, Schabus M., Noirhomme Q., Brédart S., Boly M., Phillips C., Soddu A., Luxen A., Moonen G., Laureys S. *Co-first author
Journal of Cognitive Neurosciences 2010: in press

Willful modulation of brain activity in disorders of consciousness.
Monti M.*, Vanhaudenhuyse A.*, Coleman M., Boly M., Pickard J., Tshibanda L., Owen A., Laureys S. *Co-first author
The New England Journal of Medicine 2010: 362(7), 579-589

Disorders of consciousness: moving from passive to resting state and active paradigms.
Bruno MA., Soddu A., Demertzi A., Laureys S., Gosseries O., Schnakers C., Boly M., Noirhomme Q., Thonnard M., Chatelle C., Vanhaudenhuyse A.
Cognitive Neurosciences 2010: in press

The challenge of disentangling reportability and phenomenal consciousness in post-comatose states.
Vanhaudenhuyse A., Bruno MA., Brédart S., Plenevaux A., Laureys S.
Behavioral Brain Science 2007: 30, 529-530 (letter)

Neuroimaging after coma.

Tshibanda L.*, Vanhaudenhuyse A.*, Boly M., Soddu A., Bruno MA., Moonen G., Laureys S., Noirhomme Q. *Co-first author

Neuroradiology 2010: 52(1), 15-24

Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls.

Tshibanda L.*, Vanhaudenhuyse A.*, Galanaud D., Boly M., Laureys S., Puybasset L. *Co-first author

Progress in Brain Research 2009: 177, 215-229

Parallèlement aux techniques d'EEG, l'imagerie par résonance magnétique (IRM) offre la possibilité d'étudier les corrélats neuronaux de la conscience que ce soit chez des sujets sains ou des patients en état de conscience altérée. Plusieurs méthodes existent actuellement. Certaines s'intéressent aux réponses corticales lors de stimulations sensorielles (tactiles, auditives, visuelles, etc.), d'autres proposent de mesurer l'activité neuronale au repos et de lui donner une signification en termes de conscience (Vanhaudenhuyse et al., 2010a; 2010b), d'autres encore s'intéressent aux paradigmes dits *actifs* au cours desquels des tâches cognitives d'imagerie mentale sont demandées aux participants (Monti & Vanhaudenhuyse et al., 2010). Des séquences d'IRM structurelle sont également de plus en plus étudiées quant à leur valeur diagnostique et pronostique chez des patients en état de conscience altérée (Tshibanda & Vanhaudenhuyse et al, 2009 ; 2010).

I. Resting state et état de conscience altérée : promesse d'un nouveau modèle en IRMf

Depuis quelques années, une attention croissante est portée à l'activité cérébrale spontanée, ainsi qu'à sa signification comportementale et cognitive (Raichle, 2006). En 2001, Gusnard et Raichle proposaient le nouveau concept de réseau du mode par défaut – *default mode network* – après avoir observé que la majorité des études réalisées en TEP et IRM fonctionnelle (IRMf) rapportaient, en plus des activations cérébrales liées à leurs tâches respectives, des désactivations de régions spécifiques lorsque les sujets étaient en train de réaliser ces tâches. Ces diminutions de signal sont le reflet d'une suppression des processus de traitement de l'information dans des régions cérébrales n'étant pas impliquées dans la réalisation de la tâche en cours (Drevets et al., 1995) et variant très peu quant à leur localisation (Gusnard and Raichle, 2001). Dans leurs études, pionnières en termes de réseau du mode par défaut, l'équipe de Shulman a démontré une certaine consistance au sein de ces régions cérébrales dont l'activité diminue lors de tâches cognitives attentionnelles (Shulman et al., 1997a; 1997b). Mazoyer et al. (2001) ont confirmé ces résultats en étudiant directement l'activité cérébrale résultant d'une tâche de repos au cours de laquelle les sujets recevaient comme instruction « fermez les yeux, relaxez-vous, évitez de bouger et évitez toutes pensées structurées comme chanter, compter, etc. ». Ce réseau, aujourd'hui appelé communément *réseau du mode par défaut*, comprend des régions telles que le cortex cingulaire postérieur, le précunéus, les jonctions temporo-pariétales et le cortex préfrontal. Toujours selon Gusnard et Raichle (2001), ce réseau du mode par défaut doit être vu comme la ligne de base de l'activité cérébrale. Cette activité cérébrale au repos est caractérisée par des fluctuations lentes spontanées du signal dépendant du niveau d'oxygène dans le sang (Blood Oxygen Level Dependent – BOLD), variant de 0.01 à 0.1Hz. Ces fluctuations spontanées ne peuvent pas être uniquement attribuées au bruit périphérique (par exemple, aux fluctuations cardiaques ou respiratoires, aux mouvements du sujet, etc.) mais démontrent une activité synchrone avec d'autres régions cérébrales fonctionnellement en relation (Cordes et al., 2000; Fox and Raichle, 2007). Cette activité cérébrale de base semble être organisée en deux sous réseaux; l'un étant externe, l'autre interne (Boly et al., 2007a; Cordes et al., 2000; Fox and Raichle, 2007; Fox et al., 2005; Fransson, 2005; Golland et al., 2007; Tian et al., 2007). Le réseau externe, comprenant les régions frontopariétales latérales, est activé lors de comportements dirigés vers un but, ainsi que lors de la perception de stimuli externes somatosensoriels nociceptifs (Boly et al., 2007a; Bornhovd et al., 2002; Buchel et al., 2002), visuels (Fuhrmann Alpert et al., 2008; Rees, 2007) et auditifs (Fuhrmann Alpert et al., 2008). Quant au réseau interne, il comprend principalement les aires cérébrales médiales (réseau du mode par défaut). Ce dernier est impliqué dans des processus cognitifs particuliers tels que les rêves éveillés (*day-dreaming*) ou les pensées internes (*mind-wandering* – Mason et al., 2007; McKiernan et al., 2006), l'imagerie mentale (Knauff et al., 2003), les pensées indépendantes de stimulus (Buckner et al., 2008) et le discours intérieur ou les pensées relatives à soi (Goldberg et al., 2006; Laureys et al., 2007; Lou et al., 2004). Par ailleurs, si la fonction exacte du réseau du mode par défaut est toujours au cœur de nombreux débats, certains travaux proposent que celui-ci joue un rôle de base dans le réseau neuronal de la conscience (Boly et al., 2008b; Greicius et al., 2008).

Plusieurs études réalisées chez des volontaires sains ont déjà démontré la capacité de l'IRMf à identifier les patterns neuronaux du réseau du mode par défaut (Cavanna, 2007; Cavanna and Trimble, 2006; Damoiseaux et al., 2006; Shehzad et al., 2009). Cliniquement, l'étude du réseau du mode par défaut chez des patients en état de conscience altérée permettrait d'étudier des processus cognitifs complexes qui ne requièrent pas la collaboration des patients. De plus, ce nouveau paradigme d'acquisition fonctionnelle est plus facile à appliquer que des paradigmes de stimulations classiquement employés jusqu'à présent et pourrait donc être adapté à un contexte d'examen clinique. A l'heure actuelle, la signification fonctionnelle du réseau du mode par défaut reste encore floue, certains auteurs remettent en question la valeur et les interprétations faites de ces variations spontanées de l'activité cérébrale en IRMf (Morcom and Fletcher, 2007).

Dans notre étude, nous avons analysé la connectivité du réseau du mode par défaut chez des patients en coma, état végétatif, état de conscience minimale et locked-in syndrome.

Notre hypothèse de travail était que la connectivité au sein de ce réseau était directement liée au degré de conscience de ces patients. De plus, au vu de son rôle particulier dans le réseau du mode par défaut (Fransson and Marrelec, 2008), ainsi que de son interconnectivité avec la majorité des autres aires cérébrales (Hagmann et al., 2008), nous postulions que la connectivité du précunéus serait spécifiquement en lien avec le niveau de conscience de ces patients. Nous avons acquis dix minutes de repos en IRMf chez 14 patients sévèrement cérébrolésés (1 patient en locked-in syndrome, 4 en état de conscience minimale, 4 en état végétatif et 5 en coma; âge de 25 à 77 ans – voir Vanhaudenhuyse et al., 2009b pour les détails cliniques de chaque patient), ainsi que chez 14 sujets volontaires appareillés en âge. Les diagnostics d'état de conscience altérée étaient émis suite à des évaluations comportementales (CRS-R et GCS) réalisées le jour même de l'examen par IRMf, ainsi que les semaines précédant et suivant l'examen. L'ensemble des données ont été préprocessées et analysées à l'aide du logiciel Statistical Prametric Mapping-5 (www.fil.ion.ucl.ac.uk/spm) et par une méthode d'analyse de composantes indépendantes (Beckmann and Smith, 2004) implémentée dans le logiciel MELODIC, faisant partie du Functional MRI of the Brain software library (FSL – www.fmrib.ox.ac.uk/fsl).

Tout d'abord, les résultats obtenus chez les volontaires ont permis d'identifier le réseau du mode par défaut, comprenant le cortex cingulaire postérieur/précunéus, les jonctions temporo-pariétales, le cortex préfrontal médian, les gyri parahippocamiques, les sulci frontaux supérieurs et le thalamus (Figure 5).

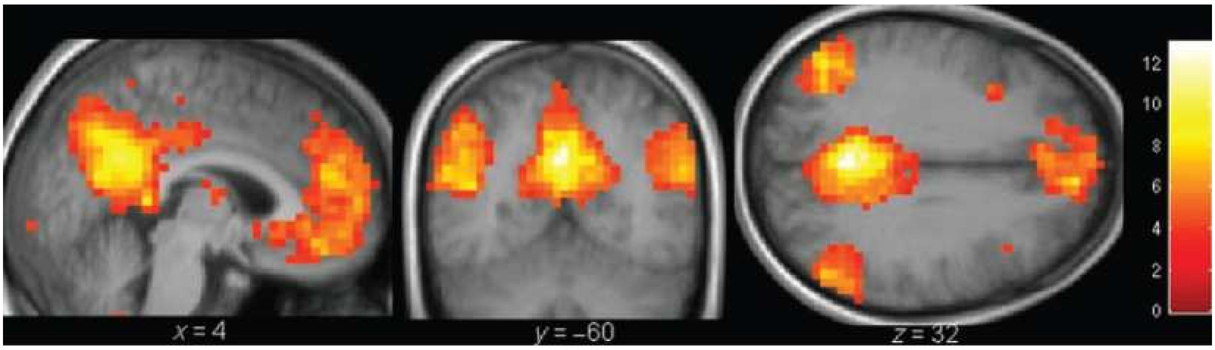


Figure 5: Réseau du mode par défaut identifié chez les volontaires (Vanhaudenhuyse et al., 2009b).

Les résultats obtenus avec un contraste non-linéaire chez les patients démontrent une corrélation entre le niveau de connectivité au sein du réseau du mode par défaut et le degré de conscience des patients dans toutes les régions identifiées chez les sujets contrôles (cortex cingulaire postérieur/précunéus, jonctions temporo-pariétales, cortex préfrontal médian, gyri parahippocampiques, sulci frontaux supérieurs, thalamus – Figure 6). D'autres contrastes nous ont permis d’identifier les mêmes régions, confirmant ainsi nos résultats obtenus chez les patients, tandis que le calcul d’un contraste linéaire, même s’il permettait d’obtenir des résultats significatifs, donnait de moins bons résultats. Ces derniers résultats ne sont, pour nous, pas surprenants, puisque dans notre pratique clinique nous savons que les différents degrés de conscience des patients ne peuvent être modélisés linéairement. En effet, le niveau de conscience des patients en état végétatif est plus proche de celui des patients en coma que de celui des patients en état de conscience minimale.

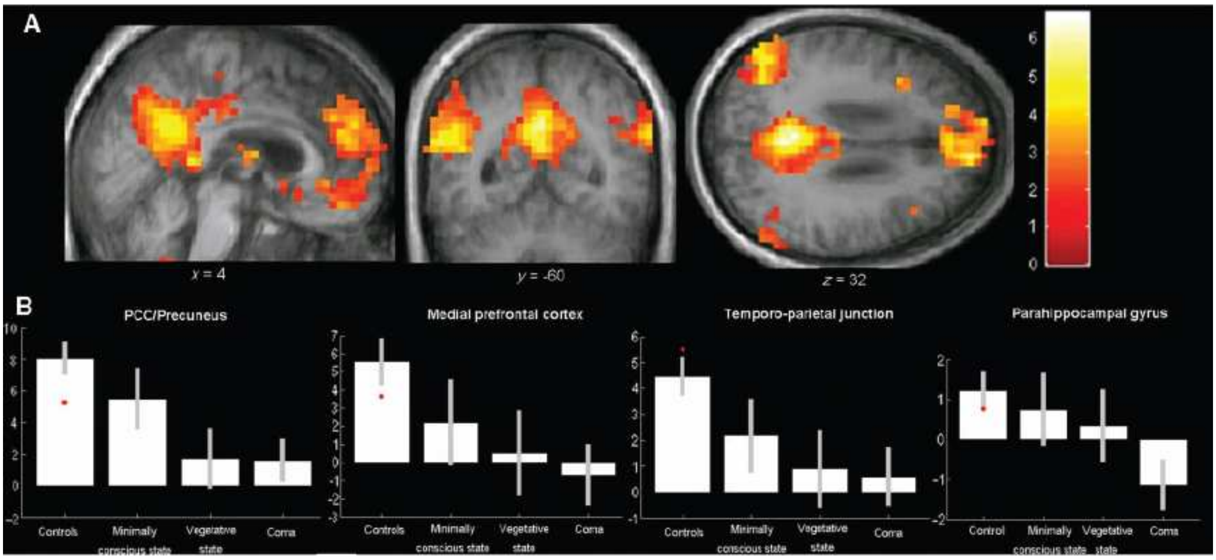


Figure 6 : (**A**) Régions cérébrales démontrant une corrélation entre le niveau de connectivité du réseau du mode par défaut et le degré de conscience des patients ($p<0.05$). (**B**) Valeur moyenne du Z et intervalles de confiance à 90% pour la connectivité du réseau du mode par défaut chez les patients, dans les régions telles que le cortex postérieur cingulaire/précunéus, les jonctions temporo-pariétales, le cortex préfrontal médian et les gyri parahippocampiques. Les résultats obtenus chez le patient en locked-in syndrome sont représentés par un point rouge sur les graphiques et ne sont pas significativement différents de ceux obtenus chez les volontaires sains. (Vanhaudenhuyse et al., 2009b)

Enfin, le niveau de significativité le plus important de corrélation entre la connectivité et le degré de conscience a été identifié dans le cortex postérieur cingulaire/précunéus. Ces résultats sont cohérents avec les résultats démontrant le rôle capital du précunéus dans l’architecture du réseau du mode par défaut, que ce soit d’un point de vue fonctionnel (Fransson and Marrelec, 2008) ou structurel (Hagmann et al., 2008). De plus, cette région permet de différencier les patients en état végétatif, des patients en état de conscience minimale (Figure 7), suggérant une relation étroite entre le niveau d’activité de cette région et le degré de conscience des patients, comme cela a déjà pu être mis en évidence dans d’autres travaux (Cavanna and Trimble, 2006; Laureys et al., 2004a). Par contre, aucune région du réseau du mode par défaut n’a été identifiée comme présentant une meilleure connectivité chez les patients inconscients que chez les patients conscients. Enfin, aucune différence significative n’a pu être mise en évidence entre le patient en locked-in syndrome et les volontaires sains.

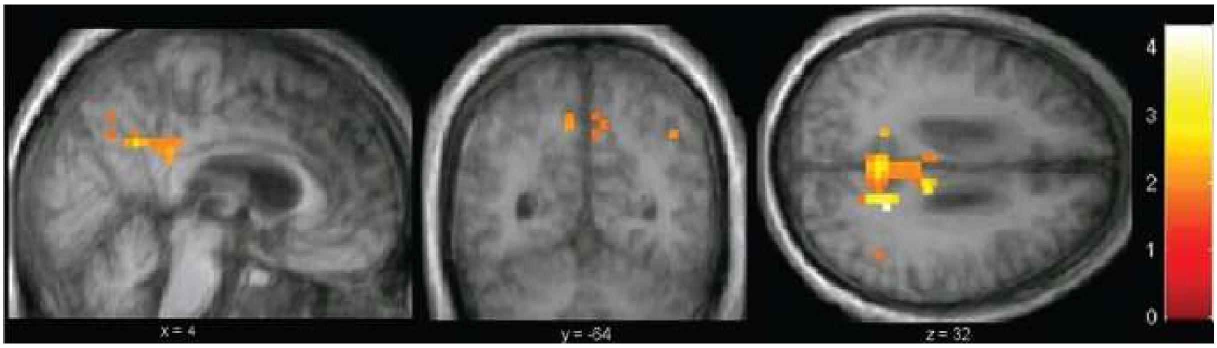


Figure 7 : Régions cérébrales du réseau du mode par défaut différenciant les patients en état de conscience minimale des patients inconscients (coma et état végétatif – $p<0.05$). (Vanhaudenhuyse et al., 2009b)

Nous avons également observé une corrélation entre la connectivité et le score total à la CRS-R dans la majeure partie du réseau du mode par défaut. Cependant, ces résultats ne survivent à une correction pour comparaisons multiples que dans le gyrus préfrontal médian. A nouveau, ces résultats obtenus en comparant le score à la CRS-R et la connectivité dans le réseau du mode par défaut sont moins probants que le calcul de contraste non-linéaire. Selon nous, cela n’a rien de surprenant puisque le score total de la CRS-R n’a pas été conçu dans le but de différencier les patients inconscients des patients conscients. Dans la CRS-R, ce sont les scores aux différentes sous-échelles qui doivent être pris en compte pour différencier les patients en état végétatif de ceux en état de conscience minimale.

Ces résultats permettent de confirmer le rôle du réseau du mode par défaut dans les processus de conscience. En effet, l’intensité de la connectivité au sein du réseau du mode par défaut identifiée en IRMf semble être quantitativement en lien avec le degré de conscience des patients sévèrement cérébrolésés. Ces résultats complètent les informations fournies par les études précédentes démontrant une préservation partielle du réseau du mode par défaut chez un patient en état végétatif (Boly et al., 2009), en sommeil léger (Horovitz et al., 2008) ou chez le singe sous anesthésie générale (Vincent et al., 2007). Ces résultats sont également en continuité avec les études récentes démontrant une diminution de la connectivité du réseau du mode par défaut chez des sujets sains sous sédation (Greicius et al., 2008) et en sommeil profond (Horovitz et al., 2009). Le même type de résultat avait pu être observé chez des patients en état végétatif isolés (Cauda et al., 2009), notre étude étant la première à avoir observé cette diminution de la connectivité au sein du réseau du mode par défaut chez une plus grande population de patients. En résumé, ces résultats mettent en évidence deux facettes importantes du réseau du mode par défaut. La première étant qu'une partie de la connectivité du réseau du mode par défaut peut persister indépendamment du niveau de conscience, ce qui pourrait refléter une connectivité anatomique sous-jacente, signe d'une dynamique cérébrale interne propre (Greicius et al., 2009; Vincent et al., 2007). La seconde, quant à elle, souligne qu'une part du réseau du mode par défaut pourrait être le reflet de processus cognitifs complexes conscients. Ces résultats sont dans la lignée des précédents résultats obtenus en TEP qui démontraient un déficit métabolique d'un large réseau fronto-pariétal chez les patients en état végétatif comparés à des sujets sains, aussi bien que dans d'autres états où le niveau de conscience est fortement perturbé tels que le sommeil, l'anesthésie, l'épilepsie ou le somnambulisme (Baars et al., 2003; Laureys, 2005b). Ces résultats sont également cohérents avec la théorie du *global workspace* de Dehaene et Changeux (2005) proposant que les régions fronto-pariétales jouent un rôle crucial dans la genèse des processus conscients. Cependant, nous devons rester prudents lors de l'interprétation de tels résultats en termes de mécanismes-clés de la conscience. D'autres études sont attendues, que ce soit sur les différents états physiologiques (le sommeil, l'hypnose), pharmacologiques (anesthésie générale), ainsi que sur les altérations pathologiques de la conscience. Ces études permettraient d'affiner les interprétations et conclusions sur le rôle du réseau du mode par défaut dans l'élaboration de la conscience. Certains travaux proposent une implication du réseau du mode par défaut dans les processus de *mind-wandering* (Mason et al., 2007) et les mécanismes autoréférentiels (Cavanna, 2007; Cavanna and Trimble, 2006). Dès lors, nos résultats pourraient suggérer que les patients en état de conscience minimale aient une conscience de soi ou une cognition de type *rêves-éveillés* partiellement préservée, ou au moins une architecture fonctionnelle résiduelle permettant le fonctionnement de ces processus. Notons également que si le thalamus n'a pas été reporté comme résultat dans l'ensemble des études sur le réseau du mode par défaut, il a tout de même été récemment décrit chez des volontaires sains (Boly et al., 2009; De Luca et al., 2006; Fransson, 2005; Greicius et al., 2007). De plus, les circuits thalamo-corticaux sont associés aux processus de perception consciente (Laureys et al., 2000c; Schiff and Fins, 2007; White and Alkire, 2003), ce qui pourrait expliquer que nous l'ayons retrouvé dans nos résultats. Cliniquement, cette étude révèle l'utilité de l'étude du réseau du mode par défaut et particulièrement de la connectivité au sein de ce réseau comme outil d'aide au diagnostic d'état de conscience altérée chez des patients sévèrement cérébrolésés.

Certains diront que même si les acquisitions en IRMf au repos sont plus faciles à réaliser chez les patients que les paradigmes de stimulations sensorielles, davantage d'artéfacts pourront être observés dans ces données que dans des données évoquées par des stimuli (Morcom and Fletcher, 2007). Pour diminuer ce biais, les analyses utilisées doivent donc inclure une méthode permettant de séparer le signal pertinent des artéfacts. C'est dans cette optique que nous avons choisi d'utiliser la technique d'analyse par composante indépendante (*Independent Component Analysis – ICA*). En effet, en comparaison à la méthode classique d'analyse par région d'intérêt (*Region Of Interest – ROI*), l'ICA offre le double avantage d'être capable d'isoler les cartes de connectivité corticale du signal non neuronal (Beckmann et al., 2005; Beckmann and Smith, 2004; Seeley et al., 2007) et de ne pas être biaisée par la sélection de régions d'intérêt pour les analyses de corrélation. De la sorte, l'ICA permet d'identifier des réseaux non identifiés par la méthode de ROI (Seeley et al., 2007). Cependant, la sélection des composantes pertinentes est toujours un problème dans les méthodes d'ICA. Une méthode automatique de sélection de composantes, telle qu'utilisée dans le présent travail, est idéale pour éviter les biais d'interprétation liés à une sélection manuelle. Dans notre étude, le modèle utilisé pour sélectionner les composantes du réseau du mode par défaut provient d'une analyse réalisée sur un groupe de sujets volontaires sains indépendants et a ensuite été appliqué au groupe contrôle ainsi qu'aux patients. Notons que, même si cette méthodologie est classiquement employée dans les études cliniques de la connectivité du réseau du mode par défaut (par exemple, chez les patients déments – Greicius et al., 2004, dépressifs – Greicius et al., 2007, ou épileptiques – Zhang et al., 2009), elle peut être source de biais quant à la sélection des composantes. Dès lors, de futures études pourraient comparer la méthode utilisée dans ce travail à d'autres méthodes de sélection afin de tester la fiabilité de chacune de ces techniques. Une dernière interrogation, toujours présente après cette étude, porte sur le lien existant entre la connectivité structurelle et fonctionnelle chez ces patients sévèrement cérébrolésés, connectivité déjà été mise en évidence chez des sujets sains (Greicius et al., 2009). Il serait donc nécessaire de réaliser des études multimodales du même genre, combinant des données de repos en IRMf avec des données d'IRM structurelle telles que des données de tenseur de diffusion ou des enregistrements d'EEG de haute densité chez les patients en état de conscience altérée.

Enfin, dans une seconde étude en IRMf, nous sommes parvenus à éclaircir les mécanismes cognitifs subjectifs sous-jacents au réseau du mode par défaut chez des volontaires sains (Vanhaudenhuyse et al., 2010a). Le paradigme de cette étude consistait à demander aux sujets d'évaluer l'intensité de leur conscience externe et interne sur une échelle de 0 à 4 (1 = intensément externe, 2 = modérément externe, 3 = modérément interne, 4 = intensément interne). Les résultats obtenus démontrent que l'intensité de la conscience interne corrèle avec l'activité des cortex postérieur cingulaire/précunéal, antérieur cingulaire/mésiofrontal et parahippocampiques bilatérales – correspondant au réseau du mode par défaut (Figure 8 – régions bleues). Quant à l'intensité de la conscience externe, elle est linéairement corrélée avec l'activité des gyri frontaux inférieurs bilatéraux et du lobe pariétal inférieur (Figure 8 – régions rouges – Vanhaudenhuyse et al., 2010a). Ces résultats ont une implication clinique directe car ils permettent une meilleure compréhension du fonctionnement cérébral des patients sévèrement cérébrolésés. En effet, le rôle critique des réseaux externe et interne de la conscience identifiés dans cette étude est illustré chez ces patients. Les patients en état végétatif, par exemple, sont caractérisés par un dysfonctionnement systématique d'un large réseau fronto-pariétal (Laureys, 2005a; Laureys et al., 1999a). Le même type d'observation a été fait chez une patiente souffrant de catatonie akinétique (De Tiege et al., 2003). De plus, des déconnections entre les régions frontales latérales et postérieures médiales, et entre les noyaux thalamiques et les cortex frontaux médians et latéraux sont également typiques chez ces patients (Laureys et al., 2000c; 1999a). Nos résultats sont également en accord avec les travaux démontrant que la perte de conscience externe et interne est observée en sommeil lent (Maquet et al., 2005) et en anesthésie générale (Kaisti et al., 2003), alors qu'elles sont restaurées en sommeil REM (Maquet et al., 2005). Nous avons également pu mettre en évidence une alternance entre la conscience externe et la conscience interne apparaissant à une fréquence moyenne de 20s (0.05Hz), ce qui correspond aux fréquences lentes déjà rapportées dans d'autres études sur le réseau du mode par défaut (Cordes et al., 2000; Fox and Raichle, 2007). Alors que certains auteurs suggèrent que les fluctuations lentes du signal au repos ne reflètent rien d'autre que des mécanismes vasculaires (Morcom and Fletcher, 2007), d'autres sont d'accord pour dire qu'elles sont en lien avec une activité mentale consciente (Goldberg et al., 2006).

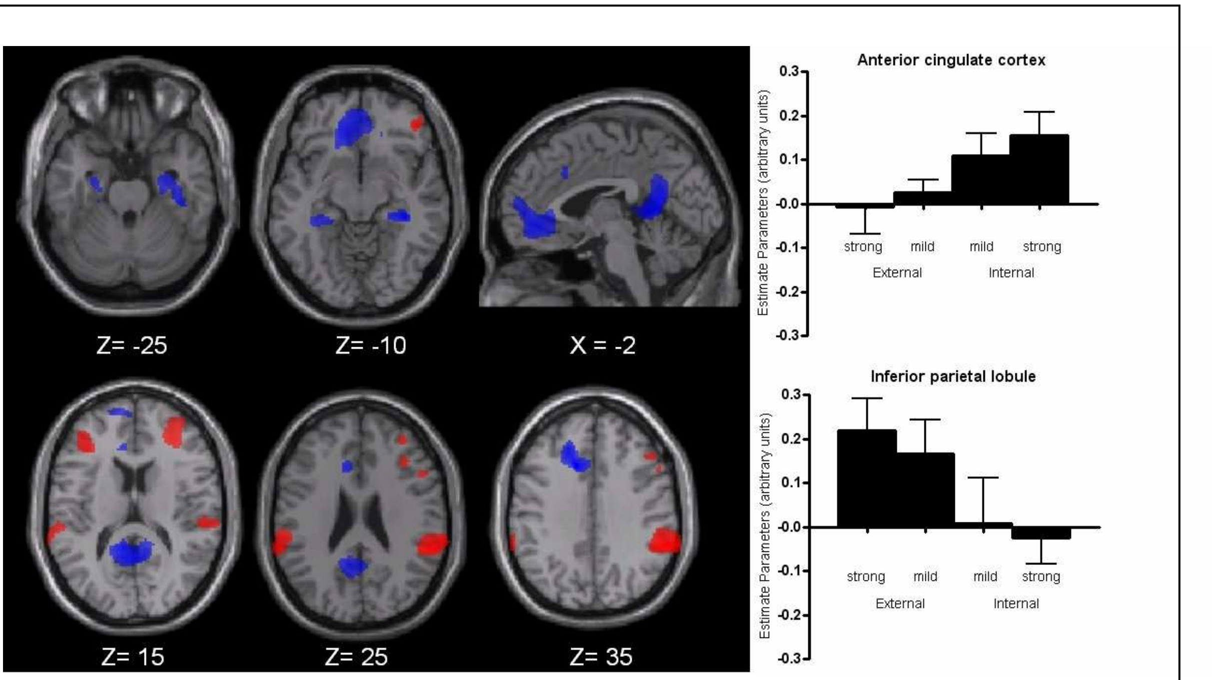


Figure 8 : Régions cérébrales démontrant une corrélation entre le signal BOLD et l'intensité des consciences externe et interne chez 22 volontaires. Un niveau élevé de conscience interne corrèle avec une augmentation de l'activité dans les cortex cingulaire postérieur/précunéal, antérieur cingulaire/mésiofrontal et parahippocampique (en bleu) ; alors que l'intensité de la conscience externe corrèle avec une augmentation de l'activité des lobes pariétaux inférieurs bilatéraux et des cortex préfrontaux dorso-latéraux (en rouge). (Vanhaudenhuyse et al., 2010a)

II. Paradigmes actifs en IRMf : quelle aide au diagnostic d'état de conscience altérée ?

L'absence de preuve n'est pas la preuve d'absence

William Cowper

1731-1800

En l'absence d'une compréhension totale des mécanismes cérébraux sous-jacents de la conscience, une activation observée chez un patient, similaire à une activation normale, ne peut pas totalement être considérée comme une preuve tangible de conscience. La seule conclusion que l'on puisse en tirer est que ces régions spécifiques sont capables de traiter les stimuli sensoriels de manière appropriée (Bruno et al., 2010). Dès lors, la question est de savoir comment distinguer une activité cérébrale automatique d'une activité volontaire consciente. Pour tenter d'y répondre, Owen et al. (2006) ont proposé d'appliquer un paradigme d'IRMf dit *actif* chez une patiente initialement diagnostiquée comme étant en état végétatif. Ils ont demandé à cette patiente de réaliser deux tâches d'imagerie mentale qui avaient été préalablement validées chez une série de volontaires sains (Boly et al., 2007b).

Lorsqu’il était demandé à la patiente de « s’imaginer jouer au tennis », une activation de l’aire motrice supplémentaire était enregistrée. Tandis qu’une activation des gyri parahippocampiques était observée lorsqu’il lui était demandé de « s’imaginer visiter sa maison ». Ces activations cérébrales, identiques à celles observées chez des volontaires sains (Boly et al., 2007b), étaient donc la preuve que la patiente, d’une part, comprenait les instructions et d’autre part, qu’elle était capable de les réaliser. Soulignons que ces activations ne pouvaient être interprétées que comme provenant d’une intention consciente de la part de la patiente puisque la seule différence entre les deux tâches proposées était la consigne donnée en début de séquence. Par ailleurs, même si les mots « tennis » et « maison » ont déjà été rapportés comme provoquant une activité cérébrale automatique – non consciente, cette activité est connue pour ne durer que quelques secondes et n’apparaît que dans des régions liées au traitement des mots (Hauk et al., 2004). Chez cette patiente, l’activité cérébrale durait l’entièreté de chaque période durant laquelle la tâche lui était demandée (30s), était localisée dans les régions connues pour leur implication dans des tâches d’imagerie motrice (Boly et al., 2007b; Weiskopf et al., 2004) et perdurait jusqu’au moment où la patiente recevait une nouvelle consigne (Owen et al., 2007). De telles réactions ne sont pas explicables en termes d’activation automatique (Soddu et al., 2010). Six mois après cette étude, la patiente démontrait des signes comportementaux de conscience. Ces résultats ne doivent donc pas être interprétés comme une évidence que tous les patients en état végétatif sont capables de réaliser des tâches d’imagerie mentale, mais plutôt comme un nouvel outil de détection de la conscience sans entrave motrice et un nouvel outil d’évaluation pronostique. Afin d’investiguer la valeur diagnostique de ces paradigmes actifs, en collaboration avec l’Université de Cambridge, nous les avons appliqués à une population de patients en état végétatif et en état de conscience minimale scannés en IRMf entre les mois de novembre 2005 et janvier 2009. Le but de cette étude était, tout d’abord, de déterminer la proportion de patients capables de moduler leur activité cérébrale en IRM, démontrant ainsi leur conscience. Ensuite, nous désirions adapter ce paradigme actif en un système de communication par réponse oui/non, permettant ainsi aux patients de communiquer sans avoir recours aux canaux classiques de communication (moteur et langagier).

54 patients ont été inclus dans cette étude (23 en état végétatif, 31 en état de conscience minimale – pour les données cliniques des patients, voir Monti & Vanhaudenhuyse et al., 2010). Les deux tâches d’imagerie mentale précédemment décrites (Owen et al., 2006) – imaginer jouer au tennis (« imaginez les mouvements de votre corps lorsque vous jouez au tennis »), imaginer visiter sa maison (« imaginez les détails du trajet de

la porte d'entrée de votre maison jusqu'à la porte de votre chambre ») – ont été demandées à ces patients. Les deux tâches d'imagerie ont été réalisées lors de deux sessions différentes. Dans chaque session, les patients devaient alterner 30s de repos (« relaxez-vous ») et 30s d'imagerie mentale. Chaque session comportait 5 périodes de repos et 5 périodes d'imagerie mentale (pour plus de détails sur la méthodologie, voir Monti & Vanhaudenhuyse et al., 2010). Parmi les 54 patients, 5 (4 en état végétatif et 1 en état de conscience minimale) ont démontré une activité consistante avec les tâches d'imagerie mentale proposées. Chez ces 5 patients (patients B-F, Figure 9), une activité cérébrale spécifique a pu être mise en évidence dans l'aire motrice supplémentaire lorsqu'ils devaient réaliser la tâche d'imagerie motrice (jouer au tennis). Chez 4 d'entre eux (B-D, F, Figure 9), une activité cérébrale spécifique a pu être mise en évidence dans le gyrus parahippocampique lors de la tâche visuo-spatiale.

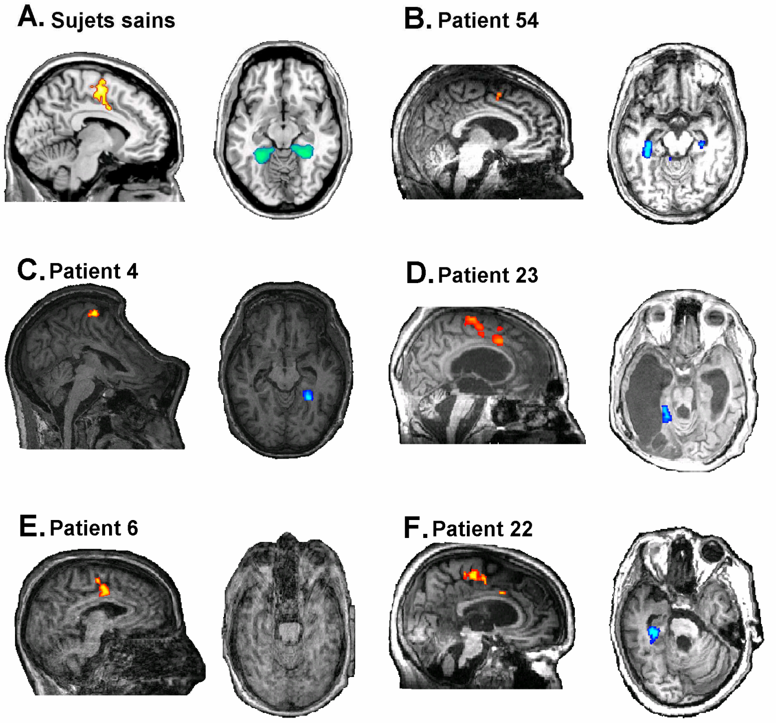


Figure 9 : Activations obtenues chez 16 volontaires sains **(A)** ainsi que chez 5 patients d'étiologie traumatique **(B-F)** lors de deux tâches d'imagerie mentale : imaginez jouer au tennis (jaune et rouge), imaginer visitez votre maison (vert et bleu). (Monti & Vanhaudenhuyse et al., 2010)

De plus, la durée de ces activations cérébrales était de 30s, c'est-à-dire l'entièreté de chaque période durant lesquelles les tâches devaient être réalisées, le début de ces activations coïncidant au moment où l'instruction était délivrée (Figure 10). L'ensemble de ces résultats obtenus chez les patients sont similaires à ceux obtenus chez les sujets contrôles. Tous étaient d'étiologie traumatique, et 4 d'entre eux étaient diagnostiqués comme étant en état végétatif (patient 4 décrit par Owen et al., 2006). Quant à la tâche de communication par oui/non en modulant l’activité cérébrale, elle a d’abord été validée chez 16 sujets contrôles, pour être ensuite appliquée à un patient. Ce dernier avait reçu le diagnostic d’état végétatif 17 mois après son accident traumatique. Ce diagnostic avait été confirmé par un bilan réalisé 3.5 ans après son accident. Lorsqu’il est arrivé au Centre Hospitalier Universitaire de Liège pour un bilan complet de conscience (5 ans post-trauma), ce diagnostic était toujours d’actualité. Lors de cette semaine d’évaluation, durant laquelle l’IRMf a été réalisée, les évaluations comportementales ont révélé des signes de conscience reproductibles traduisant un état de conscience minimale. Cependant, aucune communication n’était possible. Lors de l’IRMf, le patient s’est vu poser différentes questions d’ordre biographique (« Est-ce que ton papa s’appelle Thomas ? »), et devait répondre par « oui » en s’imaginant jouer au tennis, ou par « non » en s’imaginant visiter sa maison. Soulignons que les expérimentateurs ne connaissaient par les réponses correctes. Une seule question était posée par période d’acquisition. Durant chaque session d’acquisition, les participants (contrôles et patient) devaient alterner repos et imagerie mentale (réponse à la question). Une session d’acquisition précédait les sessions-questions afin de localiser précisément les activations cérébrales liées aux deux tâches d’imagerie. Chez les 16 sujets contrôles, les réponses aux 48 questions posées ont pu être décodées par les expérimentateurs avec 100% de justesse. Leurs patterns d’activation durant les sessions-questions étaient similaires aux patterns observés lors des sessions de localisation (Figures 10B, 10D, 11B et 11D pour une illustration chez 1 sujet). La figure 12B illustre l’intensité de l’activation chez un sujet contrôle lors des séquences de localisation et de questions. A la question 1, le sujet contrôle a répondu par une activation correspondant à la tâche d’imagerie motrice, tandis qu’aux questions 2 et 3, il a répondu par une activation typique de la tâche d’imagerie spatiale. Un pattern similaire a pu être observé chez les 15 autres sujets contrôles (voir Supplementary Appendix dans Monti & Vanhaudenhuyse et al., 2010). Pour le patient chez qui ce paradigme de communication a été testé, l’activité cérébrale observée durant les sessions-questions était similaire à celle observée durant les sessions de localisation (Figure 10A, 10C, 11A et 11C). Par exemple, à la question « Est-ce que ton papa s’appelle Alexender ? », le patient répondait « oui » (réponse correcte) en activant l'aire motrice supplémentaire uniquement (spécifique de la tâche d’imagerie motrice – Figure 11A). Alors qu’à la question « Est-ce que ton papa s’appelle Thomas ? », le patient répondait « non » (réponse correcte) en activant le gyrus parahippocampique et l’aire motrice supplémentaire (spécifiques à la tâche d’imagerie spatiale – Figure 11C). Le patient a répondu correctement à 5 des 6 questions qui lui ont été posées (Supplementary Appendix dans Monti & Vanhaudenhuyse et al., 2010). Pour cette dernière question, la réponse du patient n’était pas incorrecte, mais aucune activation cérébrale n’a pu être mise en évidence dans les régions d’intérêt (Figure 12A).

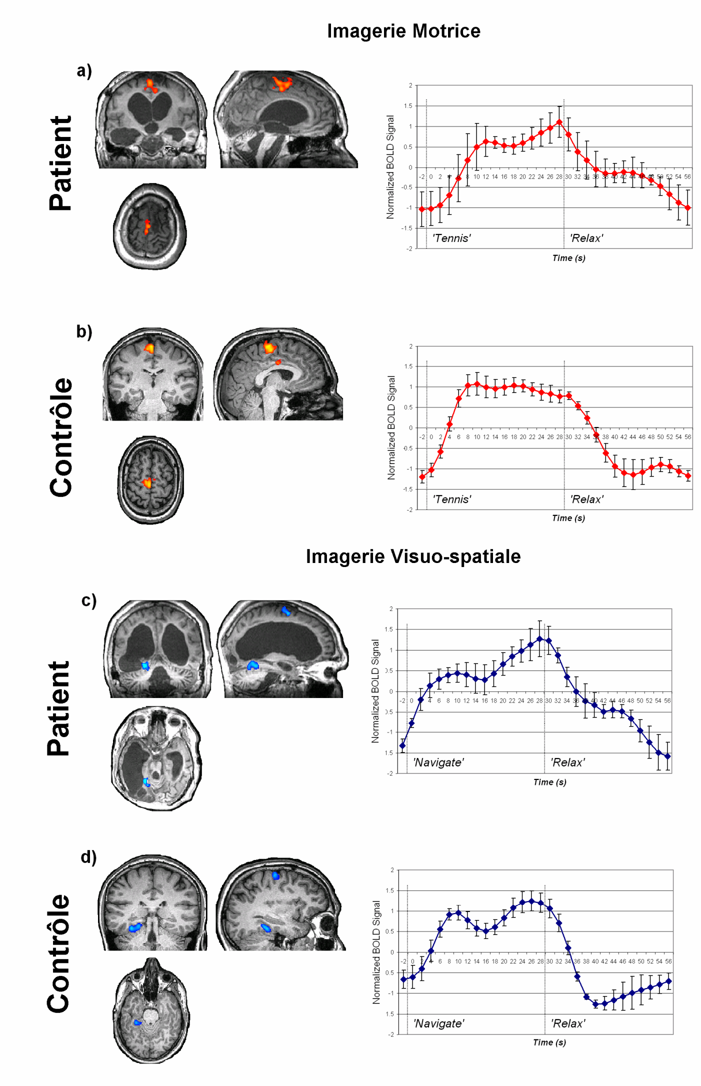


Figure 10 : (a) Activation cérébrale de l’aire motrice supplémentaire obtenue pour le patient 23 et **(b)** un sujet contrôle lors de la tâche d’imagerie motrice (imaginez jouer au tennis), comparée aux périodes de repos (relaxez-vous) ; ainsi que la courbe temporelle du voxel le plus activé dans cette région. **(c)** Activation cérébrale du gyrus parahippocampique obtenue pour le patient 23 et **(d)** un sujet contrôle lors de la tâche d’imagerie spatiale (imaginez visiter votre maison), comparée aux périodes de repos (relaxez-vous) ; ainsi que la courbe temporelle du voxel le plus activé dans cette région. (Monti & Vanhaudenhuyse et al., 2010)

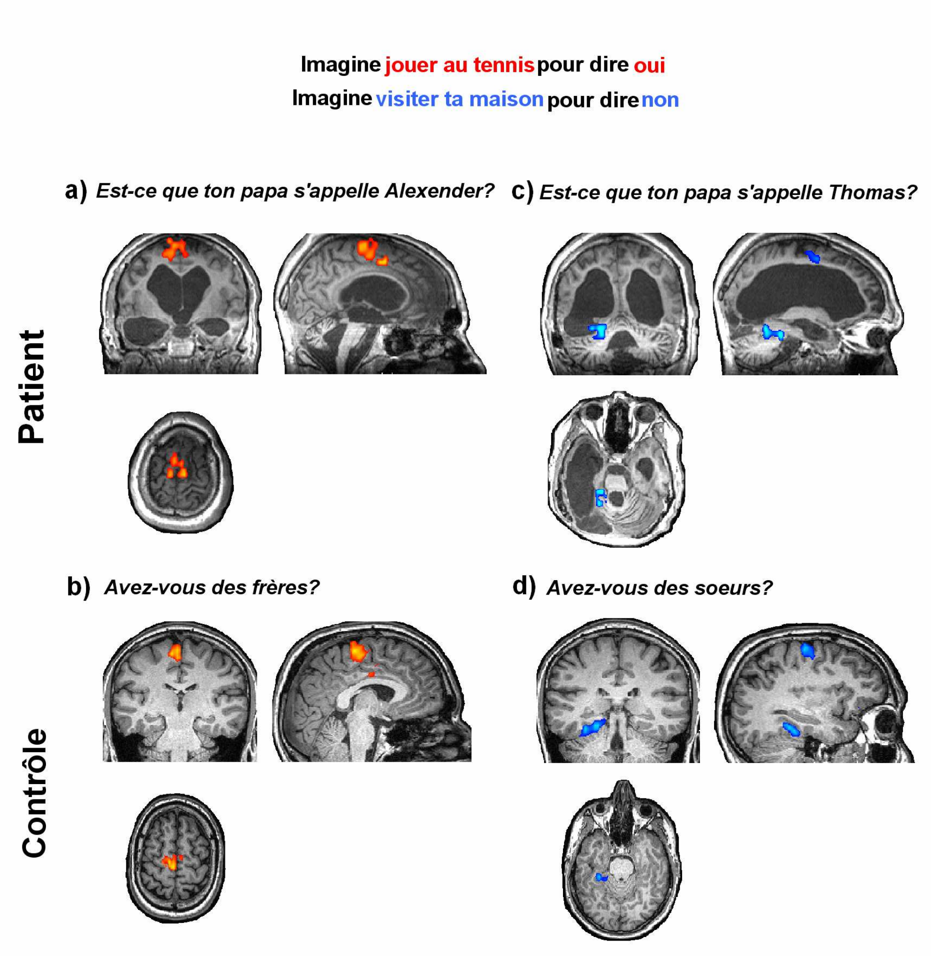


Figure 11 : Résultats obtenus pour deux sessions de questions chez le Patient 23 **(a-c)** et chez un sujet contrôle **(b-d)**. Les images **a** et **b** démontrent une activité cérébrale similaire à celle obtenue lors de la tâche d'imagerie motrice (aire motrice supplémentaire), traduisant une réponse « oui ». Les images **c** et **d** démontrent une activation similaire à celle obtenue lors de la tâche d'imagerie spatiale (gyrus parahippocampique et aire motrice supplémentaire), traduisant une réponse « non ». (Monti & Vanhaudenhuyse et al., 2010)

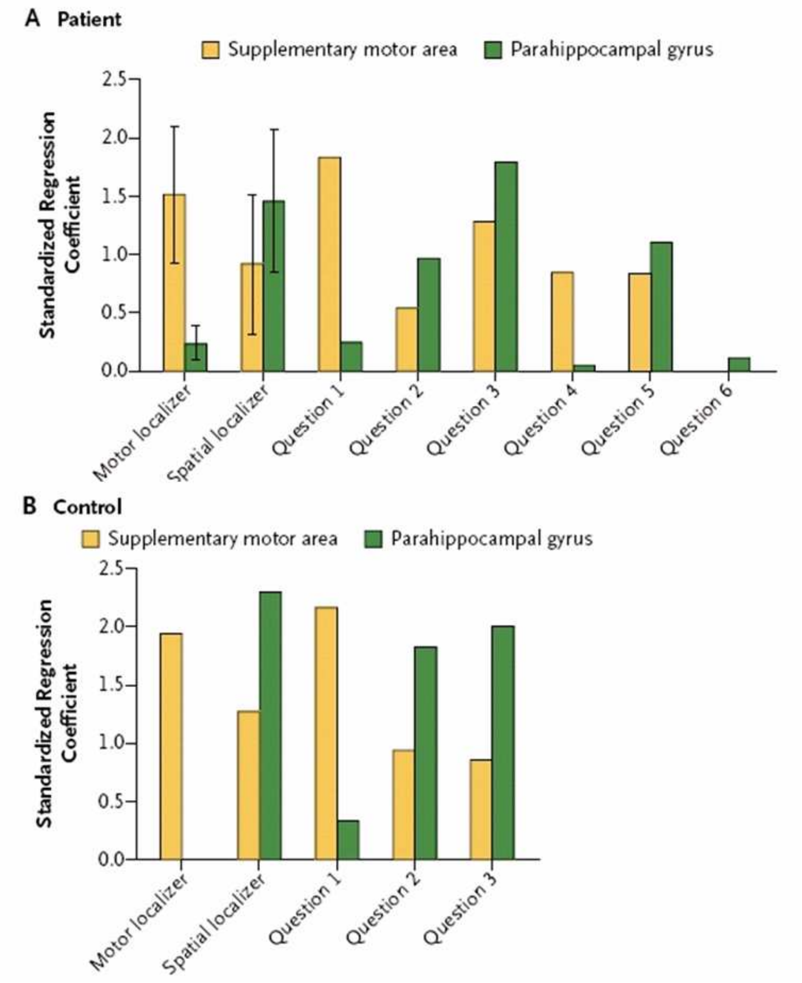


Figure 12 : Patterns d'activation dans les régions d'intérêt (aire motrice supplémentaire, gyrus parahippocampique), lors des sessions de localisation et de communication pour **A** un patient et **B** un sujet contrôle. (Monti & Vanhaudenhuyse et al., 2010)

Sur les 5 patients chez qui les tâches d'imagerie mentale ont donné des résultats positifs, 4 d'entre eux étaient initialement diagnostiqués comme étant en état végétatif. De ces 4 patients, 2 démontraient des signes de conscience lors des évaluations comportementales, alors que les 2 autres n'ont pu manifester d'aucune autre manière que par l'IRMf leur conscience, et ce malgré des évaluations comportementales répétées. Il semblerait donc qu'une minorité de patients répondant aux critères de l'état végétatif puissent avoir des fonctions cognitives et une conscience résiduelles (Monti et al., 2009; Owen and Coleman, 2008). Par ailleurs, nous avons démontré qu'il était possible de communiquer via IRMf avec un de ces patients. Malgré des signes clairs de conscience lors d'évaluations comportementales, ce patient ne démontrait aucune capacité de communication qu'elle soit verbale ou gestuelle. Grâce à cette technique de code *oui/non* et d'imagerie mentale, ce patient a pu répondre correctement à 5 questions sur 6. L'absence d'activation spécifique à l’une des tâches d’imagerie mentale pour une des questions peut se voir expliquée de différentes manières. Est-ce que le patient était plus somnolent ou endormi, avait-il bien entendu/compris la question, ou n’a-t-il simplement pas fait l’effort de répondre à la question, sont autant de suppositions qui peuvent être faites. L’interprétation de ces résultats quant à une erreur diagnostique doit cependant être prise avec précaution. En effet, il est tout à fait plausible que ce patient ait été en état végétatif durant les années précédant l’IRMf pour ensuite évoluer. Il est également probable qu’il n’ait jamais été capable de démontrer sa conscience. Dans ce cas, on ne pourrait pas réellement parler d’erreur diagnostique puisque comportementalement ce patient ne répondait à aucun critère d’état de conscience minimale. Certains pourraient dire que les activations observées étaient d’ordre automatique (Greenberg, 2007; Nachev and Husain, 2007) ou qu’elles n’avaient aucun lien avec une activité consciente de la part des patients (Gawryluk et al., 2010). Cependant, les activations observées lors des tâches simples d’imagerie mentale étaient localisées dans les régions cérébrales connues pour leur implication dans ces processus (Boly et al., 2007b; Weiskopf et al., 2004), duraient 30s (c’est-à-dire la durée complète de l’exercice) et n’apparaissaient qu’au moment où la consigne était donnée aux patients. Quant aux activations observées lors de la tâche de communication, elles apparaissaient alors que seuls les mots « réponse » ou « relaxez-vous » étaient donnés comme consigne au patient, aucun lien n’ayant été fait avec les tâches d’imagerie mentale à réaliser. Les réponses cérébrales observées ne dépendaient donc que de la décision consciente du patient sur le type de réponse qu’il voulait communiquer.

Par ailleurs, 49 patients sur 54 n’ont pas démontré d’activations cérébrales similaires à celles de sujets contrôles lors des tâches d’imagerie mentale. Il est cependant difficile de déterminer si cette absence est le résultat d’un manque de sensibilité de la méthode employée ou si elle reflète une incapacité ou une limitation cognitive de la part des patients. Certains patients pouvaient, en effet, être inconscients durant les sessions d’IRMf. Pour d’autres, en état de conscience minimale, les tâches étaient cognitivement trop complexes pour pouvoir être réalisées. En effet, des déficits des processus de compréhension du langage, de mémoire de travail, de prise de décision ou de fonctions exécutives sont autant de facteurs pouvant entraver la réussite de telles tâches. Inversement, la capacité des patients à réaliser ces tâches démontre une préservation de ces processus cognitifs. Cette étude met en évidence un moyen de détection des dissociations qui peuvent exister entre les comportements observés au chevet des patients et leur activité cérébrale résiduelle reflétant des fonctions cognitives préservées (Laureys et al., 2004a; Monti et al., 2009; Owen and Coleman, 2008). Ces résultats mettent en exergue que les déficits moteurs peuvent parfois être si importants qu’ils vont totalement empêcher le patient de démontrer sa conscience et donc empêcher l'examinateur de l'observer. Ces techniques dites *actives* doivent donc être considérées comme un outil d'aide au diagnostic chez les patients sévèrement cérébrolésés.

Certaines théories postulent qu'une conscience ne peut être présente que si le sujet peut rapporter cette conscience (pour une revue, voir Block, 2007). Si l'on s'en tient à ce genre de postulat, la conscience n'existe pas chez les patients incapables de communiquer, par exemple chez des patients en état de conscience minimale ou en locked-in syndrome complet. Les techniques telles que des paradigmes actifs en IRMf ou en EEG permettent de réfuter totalement ce type de propos. En effet, la conscience n'est pas un état qui disparaît soudainement si la personne devient incapable de la rapporter que soit de manière verbale ou motrice. 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 quotidien sont actuellement de plus en plus développées (pour une revue, voir Kübler, 2009). 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 (Kubler and Neumann, 2005). 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 pourront grâce à un système adapté en EEG (Birbaumer et al., 1999; Hinterberger et al., 2005; Kübler, 2009). Un autre exemple de BCI est le système de manipulation mentale du pH salivaire, également utilisé chez certains patients atteints de locked-in syndrome (Wilhelm et al., 2006). La figure 13 est une illustration graphique de ce type de communication *oui* (« Imaginez le goût du citron ») / *non* (« Imaginez le goût du lait ») obtenu chez un sujet volontaire.

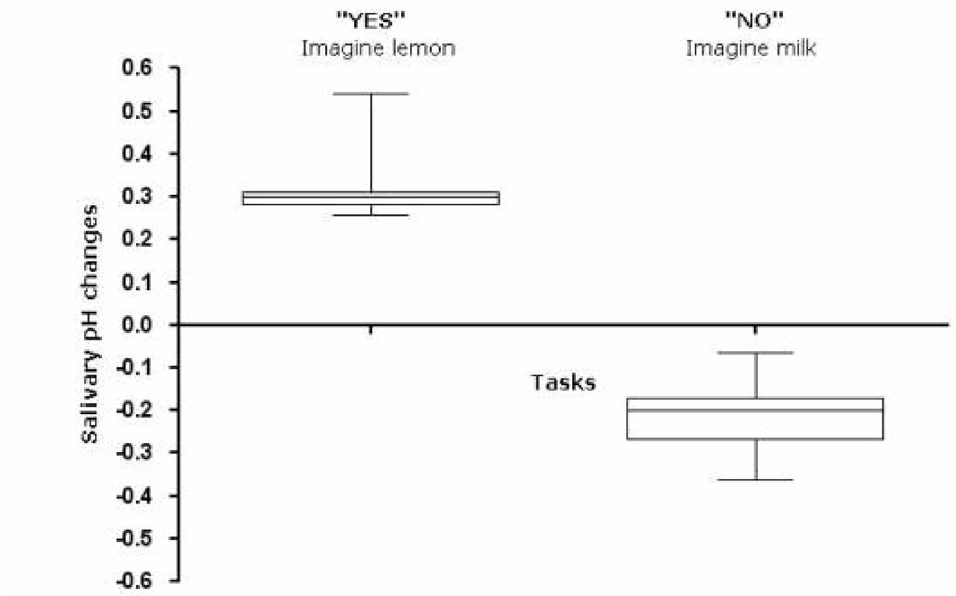


Figure 13 : Réponses non-verbales obtenues chez un sujet sain par la manipulation de son pH salivaire. Le sujet répondait « oui » en imaginant le goût du citron et « non » en imaginant le goût du lait. Les box (moyenne et déviation standard) et les barres (minimum et maximum) illustrent les réponses obtenues durant une session sans entraînement (2 minutes d'imagerie mentale pour chaque réponse). (Vanhaudenhuyse et al., 2007a)

III. Imagerie par tenseur de diffusion et spectroscopie : nouveaux outils pronostiques ?

Si l'on a précédemment vu la difficulté d'émettre un diagnostic précis et correct d'état végétatif et de conscience minimale, on comprend aisément que ces questionnements en engendrent d'autres concernant la prise en charge du patient. Comme nous avons compris que les techniques de neuroimagerie telles que l'IRMf pouvaient être d'une aide précieuse quant au diagnostic d'état de conscience altérée, d'autres séquences, récemment adaptées aux patients en état de conscience altérée, pourraient apporter leur contribution lors de prise de décisions thérapeutiques. Nous proposons ici de présenter ces techniques de spectroscopie par résonance magnétique et d'imagerie par tenseur de diffusion dans l'évaluation des patients sévèrement cérébrolésés, d'origine traumatique (Tshibanda & Vanhaudenhuyse et al., 2009; 2010).

Imagerie par tenseur de diffusion

Le principe de l'imagerie par tenseur de diffusion (*Diffusion Tensor Imaging – DTI*) se base sur les mouvements des molécules d'eau dont la diffusion est contrainte par l'organisation des tissus (Figure 14). Cette diffusion permet de mesurer la direction des faisceaux de la matière blanche et leur intégrité structurelle. En plus de l'évaluation des faisceaux, la DTI permet de mesurer la fraction d'anisotropie, c'est-à-dire de quantifier l'anisotropie de diffusion dans le cerveau, qui est en lien avec la densité, l'intégrité et la directionnalité des axones de matière blanche (Huisman et al., 2006; Jones et al., 2000). La DTI donne un aperçu de l'organisation architecturale des faisceaux de matière blanche et permet de détecter les lésions axonales éventuelles après un traumatisme crânien (Huisman et al., 2003). La DTI a plusieurs avantages : elle permet d'évaluer l'ampleur d'un traumatisme crânien chez des patients sédatés et elle n'est pas influencée par la sédation. Actuellement, les protocoles d'acquisition, de processing d'images, d'analyse et d'interprétation de la DTI sont surtout utilisés dans les routines cliniques liées à l'exploration tumorale. Cependant, des études sur les lésions axonales (Arfanakis et al., 2002; Huisman et al., 2003; Xu et al., 2007), ainsi que sur d'autres pathologies telles que le virus d'immunodéficience humaine (Filippi et al., 2001) ont démontré que la DTI pouvait détecter des lésions passées inaperçues sur des séquences d'IRM conventionnelles. La DTI, en comparaison à d'autres séquences d'IRM conventionnelles, permet également de mieux caractériser le degré d'atteinte neurologique (Shanmuganathan et al., 2004). Plusieurs études ont démontré que la DTI était sensible aux lésions des tissus qui pouvaient apparaître comme normaux sur des séquences conventionnelles d'IRM (Arfanakis et al., 2002; Chan et al., 2003).

Quant aux patients traumatisés crâniens, une corrélation négative significative a été mise en évidence entre la fraction d'anisotropie dans le splenium du corps calleux et de la capsule interne et le score total à la GCS en fin d'hospitalisation (Huisman et al., 2004). Dans une des premières études combinant DTI et imagerie par spectroscopie, Tollard et al. (2009) ont observé que la fraction d'anisotropie était significativement plus basse dans tous les sites de mesure, excepté dans le pons postérieur, chez les patients présentant une mauvaise récupération. Les auteurs ont démontré qu'il était possible d'établir un pronostic de non-récupération après 1 an avec une sensibilité de 86% et une spécificité de 97% lorsque ces deux types de séquences étaient prises en compte. La non-récupération de ces patients traumatisés crâniens était également corrélée avec une diminution de la fraction d'anisotropie dans les pédoncules cérébraux, la partie postérieure de la capsule interne, le corps calleux postérieur et les faisceaux longitudinaux inférieurs (Perlbarg et al., 2009). Ces études démontrent l'utilité de la DTI comme outil d'aide au pronostic de récupération de conscience des patients. Par ailleurs, la DTI a permis de mettre en évidence une reconstruction axonale chez un patient ayant émergé de son état de conscience minimale deux ans après son accident traumatique (Voss et al., 2006).

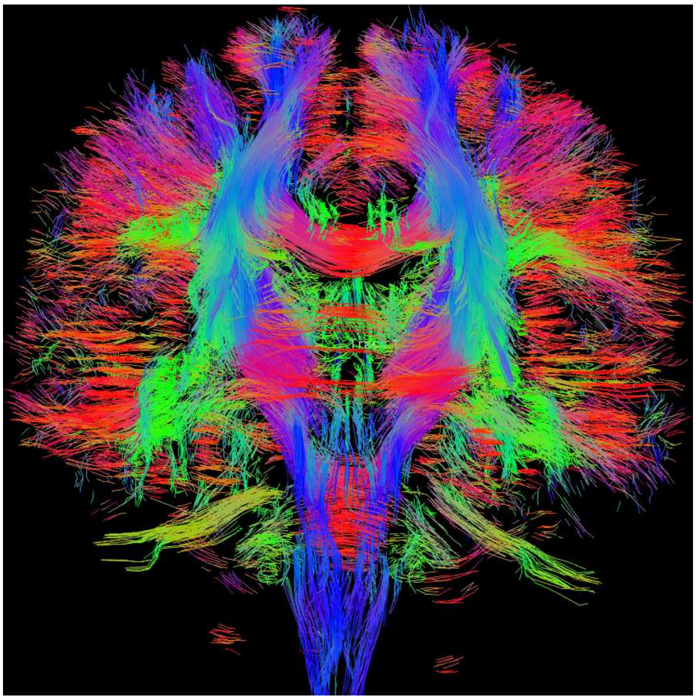


Figure 14 : Illustration des faisceaux de matière blanche lors d'une séquence d'imagerie par tenseur de diffusion chez des sujets volontaires (représentation des axes : bleu = z, rouge = x, vert = y) (Tshibanda & Vanhaudenhuyse et al., 2009).

Imagerie par spectroscopie

L'imagerie par spectroscopie (*Magnetic Resonance Spectroscopy – MRS*) est une méthode non-invasive permettant d'obtenir des informations métaboliques sur les dommages cérébraux, qui, comme pour celles mises en évidence avec la séquence DTI, ne sont pas toujours visibles sur les images morphologiques. Les métabolites tels que la choline (Cho), la créatinine (Cr), le *N*-acétylaspartate (NAA) et le lactate (La) sont classiquement étudiés lors de l'exploration par MRS des patients en état de conscience altérée. Selon Tollard et al. (2009), l'évaluation par MRS de patients post-coma devrait inclure une séquence de spectroscopie globale (*Chemical Shift Imaging – CSI*) au niveau des ganglions de la base (incluant le thalamus, le cortex insulaire et la matière blanche péri-ventriculaire), ainsi qu'une séquence mono-voxel (*Single Voxel Spectroscopy – SVS*) localisée sur la partie postérieure du pons (Figure 15). Trois raisons expliquent que la SVS soit réalisée au niveau du pons: (1) il contient une grande part du système activateur réticulaire ascendant, (2) il est souvent touché par des lésions axonales indétectables par d'autres séquences d'IRM structurelle, (3) il peut être atteint aussi bien par des lésions primaires que secondaires (Carpentier et al., 2006). Des résultats suggèrent que ces séquences apportent des informations quant au pronostic. Une étude de cas, d'un patient traumatisé crânien, démontre que le ratio de NAA/Cr était corrélé à la récupération du patient, tandis qu’aucun lien n’avait pu être observé avec d’autres ratios tels que le Cho/Cr (Choe et al., 1995). De plus, le ratio NAA/Cr permettrait de différencier les patients qui récupèrent de ceux qui ne récupèrent pas de conscience (Ricci et al., 1997). La récupération des patients traumatisés crâniens a également pu être corrélée au ratio NAA/Cr dans les matières grise et blanche des régions occipito-pariétale (Friedman et al., 1999; Ross et al., 1998), frontale (Garnett et al., 2000), thalamique (Uzan et al., 2003) et dans le splenium du corps calleux (Sinson et al., 2001). Une MRS centrée sur le pons et enregistrée en phase aiguë semble aussi permettre de différencier les patients qui vont récupérer de ceux souffrant d’un déficit neurologique persistant, en état végétatif ou décédés (Carpentier et al., 2006).

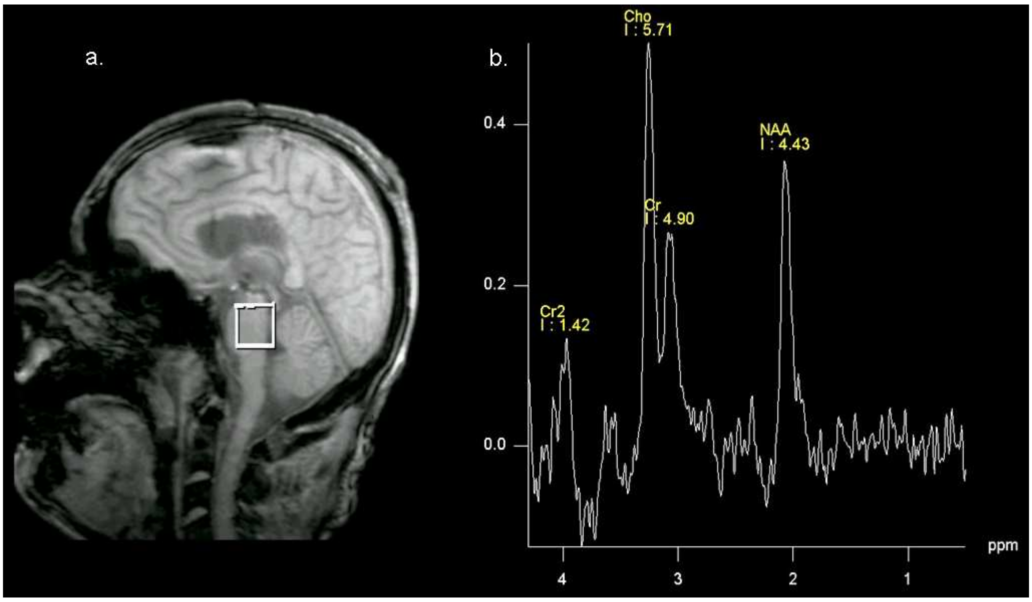


Figure 15 : Spectroscopie mono-voxel (SVS) enregistrée au niveau du pons chez un patient en état de conscience altérée suite à un traumatisme crânien : **a.** Localisation du voxel d’intérêt; **b.** illustration d’une diminution du spectre NAA (NAA/Cr = 0.90, NAA/Cho+Cr+NAA = 0.29) (Tshibanda & Vanhaudenhuyse et al., 2009).

Une évaluation par MRS devrait donc être ajoutée au bilan classique d’IRM proposé aux patients. Les diverses études démontrent que ces séquences ont leur utilité dans l’évaluation de la sévérité de l’accident cérébral et du pronostic de récupération, et permettront donc d’adapter la prise en charge des patients (voir Tableau 1, Tshibanda & Vanhaudenhuyse et al., 2009). Cependant, comme le souligne Weiss et al. (2007), les résultats de ces différentes études sont hétérogènes en termes de type de patients étudiés, de temps passé entre le traumatisme et la MRS, de voxels d’intérêt étudiés, de méthode d’évaluation de la récupération, et du moment où la récupération a été évaluée. Malgré ces données disparates, le ratio NAA/Cr normal enregistré dans les mêmes régions est similaire dans toutes les études et sa diminution semble être un bon indicateur de mauvaise récupération.

IV. Conclusion

L'incertitude des équipes médicales quant au diagnostic et au pronostic des patients survivant à un coma a des implications éthiques importantes (Bernat, 2009b). Des informations les plus exactes possibles quant au diagnostic et au pronostic sont également primordiales pour les proches des patients qui pourront plus facilement accepter les décisions médicales si ces dernières se basent sur des certitudes scientifiques. Les limites des évaluations comportementales doivent donc nous pousser à travailler en parallèle avec d'autres mesures plus objectives de détection de la conscience, afin de permettre aux cliniciens de prendre des décisions adéquates.

Les résultats obtenus dans ces différentes études démontrent l'intérêt de techniques telles que l'IRMf comme outil d'aide au diagnostic d'état de conscience altérée et l'IRM structurelle, spécifiquement des séquences comme la DTI et la MRS, pour établir des valeurs pronostiques de récupération d'une conscience. L'IRMf, que ce soit par des paradigmes au repos (Vanhaudenhuyse et al., 2010a-b) ou des tâches actives (Monti & Vanhaudenhuyse et al., 2010), permet de détecter une conscience résiduelle (Owen et al., 2006) et une relative préservation des fonctions cognitives (Coleman et al., 2007; Laureys et al., 2002; Monti et al., 2009a; Schnakers et al., 2008c) sans avoir à passer par les voies d'expression motrice ou langagière, et sans nécessiter la collaboration des patients dans le cas des paradigmes au repos. Ces modèles nous offrent la possibilité de différencier les patients inconscients des patients conscients et permettent de clarifier le diagnostic des patients chez qui les évaluations comportementales sont ambiguës. Nous avons également pu mettre au point un système de communication chez un patient qui était comportementalement incapable de communiquer. Grâce à cette approche, les patients pourraient s'exprimer quant à leur sensation de douleur, ce qui permettrait aux cliniciens d'adapter la prise en charge analgésique. D'autres topiques pourraient également être abordées comme la qualité de vie de ces patients et leur droit à prendre des décisions sur leur choix de vie. Les séquences de DTI et MRS, quant à elles, semblent prometteuses pour une évaluation du pronostic de patients traumatisés crâniens sévères chroniques (Tshibanda & Vanhaudenhuyse et al., 2010; 2009). En effet, elles permettent de détecter des lésions invisibles sur des séquences d'IRM classiques. Les progrès scientifiques faits dans ces domaines et leurs possibles applications cliniques, nous donnent des informations supplémentaires afin de comprendre les patients en état de conscience altérée, affiner leur diagnostic, prédire leur pronostic et donc répondre à des questions éthiques (Baumann et al., 2009). Cependant, nous sommes actuellement confrontés à des contraintes de sélection des patients, de modèles d'acquisition et de standardisation des protocoles. En effet, les acquisitions sont toujours limitées par leur sensibilité aux artéfacts de mouvements, ainsi que par le problème des patients sous respirateurs artificiels ou avec des éléments ferromagnétiques implantés. Des travaux futurs sont donc attendus afin de trouver des modèles d'acquisition adaptés à la réalité clinique de ces patients, ainsi qu'aux conditions hospitalières d'examen.

PERSPECTIVES

Evaluations comportementales

Si certains signes cliniques traduisent la présence d'une conscience préservée (réponses à des commandes, poursuite visuelle, expressions émotionnelles contingentes à des évènements spécifiques), d'autres nous laissent encore dubitatifs. Tout d'abord, considérons la fixation visuelle. 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 2s (Giacino et al., 2004). Cependant, pour certains auteurs, l'attention portée à un stimulus ne dénote la présence d'une conscience que lorsqu'elle est soutenue sur une période de l'ordre de la minute plutôt que de quelques secondes (Damasio and Meyer, 2009). De plus, cette évaluation des 2s de fixation relève de la subjectivité de l'examinateur et notre expérience clinique démontre que les fixations visuelles observées chez les patients peuvent parfois être très ambiguës. Inversement, la localisation de sons, qui est considérée comme présente si le patient oriente la tête et/ou les yeux vers l'endroit d'où provient le stimulus auditif, n'est pas considérée comme un comportement conscient (Giacino et al., 2004). Or, la réponse du patient est similaire à celle observée lors de la fixation visuelle (le patient détourne son attention d'un point de départ pendant quelques secondes). Dès lors, pourquoi ces deux comportements, similaires dans leur expression, ne sont-ils pas recensés de la même manière quant à leur valeur interprétative de conscience ? De prochaines études devront se pencher sur ces comportements actuellement utilisés pour établir un diagnostic d'état de conscience altérée, mais dont la signification reste encore ambiguë. Ces études devront idéalement combiner des techniques de neuroimagerie et des évaluations comportementales afin d'obtenir des données les plus précises possibles quant aux mécanismes neuronaux sous-jacents.

Parallèlement à ces critères établis et reconnus aujourd'hui comme signe ou non de conscience, d'autres comportements peuvent heurter notre réflexion lorsque nous devons donner un diagnostic. Nous avons été confrontés à des patients ne démontrant aucun signe de conscience tels que recensés par les *guidelines* (Giacino et al., 2002), mais étant capables de se nourrir par voie orale et non plus par sonde d'alimentation gastrostomique. Selon différents *guidelines*, la déglutition est un réflexe et est donc observable chez les patients en état végétatif (Australian Government National Health and Medical Research Council, 2003; The Multi-Society Task Force on PVS, 1994; Royal College of Physicians, 2003; Bernat, 2006). Le *Royal College of Physisians* (2003) souligne que ce type de comportement ne requiert pas une conscience. Une étude récente rapporte également que la déglutition peut être préservée au cours de crises d'absences épileptiques (Sadleir et al., 2009). Cependant, ces travaux ne se sont intéressés qu'au réflexe de déglutition salivaire et pas à la nutrition par voie orale. Seule une étude, réalisée en 2006, rapporte que la nutrition par voie orale est possible chez des patients en état de conscience minimale (Brady et al., 2006). Il serait donc intéressant d'étudier la prévalence de ce comportement chez les patients en état de conscience altérée, la présence ou l'absence combinée d'autres comportements conscients, ainsi que sa signification en termes de conscience.

Enfin, la présence d'une aphasie (de compréhension) peut engendrer une sous-estimation de la conscience de ces patients, en empêchant les patients de répondre correctement aux consignes qui leurs sont données. La prévalence des aphasies chez les patients sévèrement cérébrolésés n'est pas négligeable, touchant de 15 à 30% des patients selon l'étiologie traumatique ou non-traumatique (pour une revue, voir Majerus and Bruno et al., 2009). De plus, Majerus and Bruno et al. (2009) ont récemment démontré une diminution régionale du métabolisme cérébral dans les aires du langage chez des patients en état de conscience minimale, et ce quelle que soit l'étiologie. De nouvelles études devront donc proposer des outils de détection de ces troubles du langage chez les patients en état de conscience altérée, étant actuellement inexistants, par la combinaison de paradigmes auditifs de neuroimagerie (Boly et al., 2004; Laureys et al., 2000b; 2004b) et de tests neuropsychologiques adaptés à cette pathologie de la conscience.

Neuroimagerie IRM mutimodale

Le paradigme du réseau du mode par défaut est cliniquement intéressant puisqu'il est facile d'application (séquence d'acquisition fonctionnelle classique, 10 minutes d'acquisition) et permet d'étudier des processus cognitifs complexes sans avoir recours à la collaboration du patient (Bruno et al., 2010). Nous avons mis en évidence une corrélation non-linéaire entre le degré de conscience des patients et la connectivité au sein du réseau du mode par défaut (Vanhaudenhuyse et al., 2010b), suggérant que ce paradigme puisse être un outil d'aide au diagnostic. Cependant, cette étude n'a été réalisée que sur un nombre restreint de patients. De plus, un des problèmes majeurs de cette technique est sa sensibilité aux artéfacts de mouvements (spasmes, toux, myoclonies, etc. – Soddu et al., 2010). Les artéfacts cardio-respiratoires influencent également le signal BOLD de l'activité cérébrale spontanée (van Buuren et al., 2009). Des travaux futurs devront étudier la valeur diagnostique et pronostique du réseau du mode par défaut chez une plus large population de patients en état de conscience altérée, permettant ainsi de valider ce modèle pour une utilisation clinique individuelle. Un souci d'amélioration des acquisitions devra être au centre de ces études, par l'intégration d'une correction des artéfacts de mouvements et cardio-respiratoires directement durant l’acquisition des données. De plus, en raison des mouvements spontanés, la majorité des patients doivent être anesthésiés pour que l’examen par IRM puisse être réalisé. Dès lors, des études du réseau du mode par défaut, tout d’abord chez le sujet sain sous anesthésie, puis chez les patients en état de conscience altérée sous anesthésie, sont nécessaires pour permettre d’adapter ce paradigme combiné à une anesthésie générale à l’ensemble des patients en routine clinique. En combinant les résultats obtenus chez des patients anesthésiés et ceux obtenus chez des sujets sains anesthésiés, nous serons capables de déduire l’effet propre de l’agent anesthésiant et de le différencier des conséquences pathologiques de l’altération de conscience.

Enfin, si les données déjà obtenues par différents groupes de recherches en imagerie par tenseur de diffusion et spectroscopie sont prometteuses quant à leur possible implication dans la prise en charge pronostique des patients, celles-ci varient d’un groupe d’étude à l’autre (Tshibanda & Vanhaudenhuyse et al. 2010; 2009). Une des explications à cette hétérogénéité pourrait être le nombre de patients inclus dans ces travaux. Nous proposons donc d’étudier la valeur de ces séquences d’imagerie structurelle chez un grand nombre de patients en collaboration avec le Pr. Puybasset (Hôpital de la Pitié-Salpêtrière, Paris). L’ensemble de ces projets, qu’ils soient en IRM fonctionnelle ou structurelle, s’inscriront également dans une dynamique à long terme par une réévaluation des patients six mois et un an après leur accident afin de calculer les possibles corrélations existantes entre leur degré de récupération et les données obtenues en IRM.

En conclusion, par nos différentes études, nous avons montré que diagnostiquer la présence ou l’absence de conscience chez certains patients sévèrement cérébrolésés reste un défi. Les outils comportementaux que nous avons actuellement à notre disposition sont plus efficaces pour détecter les signes de conscience au chevet de ces patients que les premières échelles d’évaluation créées dans les années 1970 (Schnakers et al., 2006; 2008b; 2009b). Cependant, le manque de consensus à propos de la signification de certains comportements en termes de conscience (par exemple, le clignement à la menace visuelle) ou concernant les outils à employer pour évaluer ces signes de conscience (par exemple, la poursuite visuelle) sont autant de facteurs limitant la sensibilité des évaluations comportementales (Vanhaudenhuyse et al., 2008a; 2008c). Les techniques de neuroimagerie et d’électrophysiologie sont donc nécessaires comme outil objectif d’aide au diagnostic clinique. En effet, ces différentes méthodes permettent de détecter la présence d’une conscience résiduelle chez des patients incapables de l’extérioriser, sans faire appel aux canaux moteurs et verbaux. Ces techniques sont confrontées à d'autres limites, comme des déficits cognitifs surajoutés à la pathologie de la conscience ou encore une incompatibilité physique des patients à réaliser ces examens.

Malgré ces entraves, la méthode des potentiels évoqués permet de distinguer les patients en état végétatif des patients en état de conscience minimale, notamment grâce à des paradigmes *actifs* (Schnakers et al., 2009a; 2008d). Par ailleurs, les potentiels évoqués, qu'ils soient de courte ou de longue latence, semblent pouvoir donner des indications pronostiques sur la récupération de conscience des patients avec plus ou moins de fiabilité selon le potentiel étudié (Vanhaudenhuyse et al., 2008b).

L'utilisation de paradigmes actifs en IRMf permet également à certains patients de démontrer leur capacité à réaliser des tâches cognitives, faisant appel à la mémoire de travail et aux fonctions exécutives, et de la sorte leur permet d'exprimer leur conscience. Ces paradigmes actifs en IRMf ont permis d'établir un code de communication *oui/non* avec un patient incapable de communiquer oralement et gestuellement (Monti & Vanhaudenhuyse et al., 2010). De plus, différentes études ont mis en évidence des activations cérébrales atypiques chez des patients en état végétatif qui ont récupéré un certain degré de conscience (Di et al., 2008). Ces travaux mettent en évidence la valeur pronostique potentielle de l'IRMf.

En parallèle, des paradigmes d'acquisition au repos ont été développés dans le but de différencier des patients inconscients de patients conscients, sans faire appel à la collaboration des patients et sans être entravé par les déficits cognitifs sous-jacents (Boly et al., 2008c; 2009). Nous avons démontré que la connectivité au sein du réseau du mode par défaut était corrélée au degré de conscience des patients (coma, état végétatif, état de conscience minimale et locked-in syndrome – Vanhaudenhuyse et al., 2010b). Cette étude de la connectivité du réseau du mode par défaut a l'avantage d'être facile à acquérir et à adapter à une routine clinique.

Enfin, nous avons également relevé l'intérêt de séquences d'IRM telles que l'imagerie par tenseur de diffusion et la spectroscopie dans l'évaluation du pronostic des patients survivant à un coma (Tshibanda & Vanhaudenhuyse 2010; 2009). Les résultats des diverses études sont encore hétérogènes, insistant sur la nécessité de réaliser des études sur une large population de patients, ainsi que sur un besoin de consensus sur les sites d'enregistrement des marqueurs métaboliques.

L'utilisation de techniques telles que l'électrophysiologie et la neuroimagerie permet donc de détecter la conscience chez des patients parfois incapables de la démontrer comportementalement. Ces méthodes permettent également de différencier de manière plus précise les patients en état végétatif des patients en état de conscience minimale, et donc d'adapter leur traitement et prise en charge. En plus de l'importance clinique de ces travaux, ces études améliorent nos connaissances scientifiques sur les phénomènes conscients en mettant en évidence les corrélats neuronaux de la conscience chez l'être humain.

REFERENCES

Ad Hoc Committee of the Harvard Medical School, 1968. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. Jama 205, 337-340.

Alho, K., 1995. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear 16, 38-51.

Alkire, M.T., Haier, R.J., Barker, S.J., Shah, N.K., Wu, J.C., Kao, Y.J., 1995. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 82, 393-403.

Alkire, M.T., Haier, R.J., Shah, N.K., Anderson, C.T., 1997. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. Anesthesiology 86, 549-557.

Alkire, M.T., Pomfrett, C.J., Haier, R.J., Gianzero, M.V., Chan, C.M., Jacobsen, B.P., Fallon, J.H., 1999. Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. Anesthesiology 90, 701-709.

Amantini, A., Grippo, A., Fossi, S., Cesaretti, C., Piccioli, A., Peris, A., Ragazzoni, A., Pinto, F., 2005. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. Clin Neurophysiol 116, 229-235.

American Congress of Rehabilitation Medicine, 1995. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. Arch Phys Med Rehabil 76, 205-209.

Andrews, K., 2004. Medical decision making in the vegetative state: withdrawal of nutrition and hydration. NeuroRehabilitation 19, 299-304.

Anderson, D.C., Bundlie, S., Rockswold, G.L., 1984. Multimodality evoked potentials in closed head trauma. Arch Neurol 41, 369-374

Andrews, K., Murphy, L., Munday, R., Littlewood, C., 1996. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 313, 13-16.

Ansell, B.J., Keenan, J.E., 1989. The Western Neuro Sensory Stimulation Profile: a tool for assessing slow-to-recover head-injured patients. Arch Phys Med Rehabil 70, 104-108.

Arfanakis, K., Haughton, V.M., Carew, J.D., Rogers, B.P., Dempsey, R.J., Meyerand, M.E., 2002. Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am J Neuroradiol 23, 794-802.

Australian Government National Health and Medical Research Council, 2003. Post-Coma Unresponsiveness (Vegetative State): A Clinical Framework for Diagnosis. An Information Paper, Endorsed 18 December 2003.

Baars, B.J., Ramsoy, T.Z., Laureys, S., 2003. Brain, conscious experience and the observing self. Trends. Neurosci. 26, 671-675.

Barbato, G., Ficca, G., Muscettola, G., Fichele, M., Beatrice, M., Rinaldi, F., 2000. Diurnal variation in spontaneous eye-blink rate. Psychiatry Res 93, 145-151.

Bassetti, C., Mathis, J., Hess, C.W., 1994. Multimodal electrophysiological studies including motor evoked potentials in patients with locked-in syndrome: report of six patients. J Neurol Neurosurg Psychiatry 57, 1403-1406.

Bates, D., Caronna, J.J., Cartlidge, N.E.F., Knill-Jones, R.P., Levy, D.E., Shaw, D.A., Plum, F., 1977. A prospective study of nontraumatic coma: methods and results in 310 patients. Ann Neurol 2, 211-220.

Baudena, P., Halgren, E., Heit, G., Clarke, J.M., 1995. Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 94, 251-264.

Bauer, G., Gerstenbrand, F., Rumpl, E., 1979. Varieties of the locked-in syndrome. J Neurol 221, 77-91.

Baumann, A., Audibert, G., Claudot, F., Puybasset, L., 2009. Ethics review: end of life legislation--the French model. Crit Care 13, 204.

Beauchamp, T., Childress, J., 2001. Principles of Biomédical Ethics. Oxford University Press.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360, 1001-1013.

Beckmann, C.F., Smith, S.M., 2004. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 23, 137-152.

Bentivoglio, A.R., Bressman, S.B., Cassetta, E., Carretta, D., Tonali, P., Albanese, A., 1997. Analysis of blink rate patterns in normal subjects. Mov Disord 12, 1028-1034.

Berlad, I., Pratt, H., 1995. P300 in response to the subject's own name. Electroencephalogr Clin Neurophysiol 96, 472-474.

Bernat, 2009a. Brain Death. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. Elsevier, Oxford, pp. 151-162.

Bernat, J.L., 1992. How much of the brain must die in brain death? J Clin Ethics 3, 21-26; discussion 27-28.

Bernat, J.L., 2006. Chronic disorders of consciousness. Lancet 367, 1181-1192.

Bernat, J.L., 2009b. Ethical issues in the treatment of severe brain injury: the impact of new technologies. Ann N Y Acad Sci 1157, 117-130.

Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kubler, A., Perelmouter, J., Taub, E., Flor, H., 1999. A spelling device for the paralysed. Nature 398, 297-298.

Biringer, F., Anderson, J.R., 1992. Self-recognition in Alzheimer's disease: a mirror and video study. J Gerontol 47, P385-388.

Block, N., 2007. Consciousness, accessibility, and the mesh between psychology and neuroscience. Behav Brain Sci 30, 481-499; discussion 499-548.

Bohn-Derrien, L., 2005. Je parle. L'extraordinaire retour à la vie d'un locked-in syndrom, Paris.

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., Phillips, C., Peigneux, P., Maquet, P., Laureys, S., 2007a. Baseline brain activity fluctuations predict somatosensory perception in humans. Proc Natl Acad Sci USA 104, 12187-12192.

Boly, M., Coleman, M.R., Davis, M.H., Hampshire, A., Bor, D., Moonen, G., Maquet, P.A., Pickard, J.D., Laureys, S., Owen, A.M., 2007b. When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. Neuroimage 36, 979-992.

Boly, M., Faymonville, M.E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A., Lamy, M., Moonen, G., Maquet, P., Laureys, S., 2005. Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS. Neuropsychol Rehabil 15, 283-289.

Boly, M., Faymonville, M.E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., Degueldre, C., Franck, G., Luxen, A., Lamy, M., Moonen, G., Maquet, P., Laureys, S., 2004. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 61, 233-238.

Boly, M., Faymonville, M.E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., Lancellotti, P., Luxen, A., Lamy, M., Moonen, G., Maquet, P., Laureys, S., 2008a. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol.

Boly, M., Phillips, C., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., Peigneux, P., Faymonville, M.E., Maquet, P., Laureys, S., 2008b. Consciousness and cerebral baseline activity fluctuations. Hum Brain Mapp 29, 868-874.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T.T., Moonen, G., Hustinx, R., Maquet, P., Laureys, S., 2008c. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Ann N Y Acad Sci 1129, 119-129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., Boveroux, P., Garweg, C., Lambermont, B., Phillips, C., Luxen, A., Moonen, G., Bassetti, C., Maquet, P., Laureys, S., 2009. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum Brain Mapp 30, 2393-2400.

Born, J.D., 1988. The Glasgow-Liège Scale. Prognostic value and evaluation of motor response and brain stem reflexes after severe head injury. Acta Neurochir 95, 49-52.

Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., Buchel, C., 2002. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125, 1326-1336.

Boveroux, P., Kirsch, M., Boly, M., Massion, P., Sadzot, B., Lambermont, B., Lancellotti, P., Piret, S., Damas, P., Damas, F., Moonen, G., Laureys, S., Ledoux, D., 2008. Neurologic prognosis assessment in postanoxic encephalopathy. Réanimation 17, 613-617.

Brady, S.L., Darragh, M., Escobar, N.G., O'Neil, K., Pape, T.L., Rao, N., 2006. Persons with disorders of consciousness: are oral feedings safe/effective? Brain Inj 20, 1329-1334.

Brédart, S., Delchambre, M., Laureys, S., 2006. One's own face is hard to ignore. Q J Exp Psychol 59, 46-52.

Breen, N., Caine, D., Coltheart, M., 2001. Mirrored-self misidentification: two cases of focal onset dementia. Neurocase 7, 239-254.

Bruno, M.A., Pellas, F., Schnakers, C., Van Eeckhout, P., Bernheim, J., Pantke, K.H., Damas, F., Faymonville, M.E., Moonen, G., Goldman, S., Laureys, S., 2008. [Blink and you live: The locked-in syndrome.]. Rev Neurol (Paris) 164, 322-335.

Bruno, M.A., Schnakers, C., Damas, F., Pellas, F., Lutte, I., Bernheim, J., Majerus, S., Moonen, G., Goldman, S., Laureys, S., 2009. Locked-in syndrome in children: report of five cases and review of the literature. Pediatr Neurol 41, 237-246.

Bruno, M., Soddu, A., Demertzi, A., Laureys, S., Gosseries, O., Schnakers, C., Boly, M., Noirhomme, Q., Thonnard, M., Chatelle, C., Vanhaudenhuyse, A. 2010. Disorders of consciousness: moving from passive to resting state and active paradigms. Cognitive Neurosciences in press.

Buchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., 2002. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J Neurosci 22, 970-976.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124, 1-38.

Bundesen, C., Kyllingsbaek, S., Houmann, K.J., Jensen, R.M., 1997. Is visual attention automatically attracted to one's own name? Percept Psychophys 59, 714-720.

Calder, A.J., Lawrence, A.D., Young, A.W., 2001. Neuropsychology of fear and loathing. Nat Rev Neurosci 2, 352-363.

Cant, B.R., Hume, A.L., Judson, J.A., Shaw, N.A., 1986. The assessment of severe head injury by short-latency somatosensory and brain-stem auditory evoked potentials. Electroencephalography & Clinical Neurophysiology 65, 188-195.

Cant, B.R., Hume, A.L., Judson, J.A., Shaw, N.A., 1986. The assessment of severe head injury by short-latency somatosensory and brain-stem auditory evoked potentials. Electroencephalography & Clinical Neurophysiology 65, 188-195.

Carpentier, A., Galanaud, D., Puybasset, L., Muller, J.C., Lescot, T., Boch, A.L., Riedl, V., Cornu, P., Coriat, P., Dormont, D., van Effenterre, R., 2006. Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". J Neurotrauma 23, 674-685.

Carter, B.G., Butt, W., 2001. Review of the use of somatosensory evoked potentials in the prediction of outcome after severe brain injury. Crit Care Med 29, 178-186.

Carter, B.G., Butt, W., 2005. A prospective study of outcome predictors after severe brain injury in children. Intensive Care Med 31, 840-845.

Cauda, F., Micon, B.M., Sacco, K., Duca, S., D'Agata, F., Geminiani, G., Canavero, S., 2009. Disrupted intrinsic functional connectivity in the vegetative state. J Neurol Neurosurg Psychiatry 80, 429-431.

Cavanna, A.E., 2007. The precuneus and consciousness. CNS Spectr 12, 545-552.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564-583.

Cavinato, M., Freo, U., Ori, C., Zorzi, M., Tonin, P., Piccione, F., Merico, A., 2009. Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Inj 23, 973-980.

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J.P., Berry, I., Nespoulous, J.L., Chollet, F., 1999. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. Neuroimage 9, 135-144.

Chan, Y.L., Chu, W.C., Wong, G.W., Yeung, D.K., 2003. Diffusion-weighted MRI in shaken baby syndrome. Pediatr Radiol 33, 574-577.

Chatelle, C., Schnakers, C., Bruno, M., Gosseries, O., Laureys, S., Vanhaudenhuyse, A., 2010. The Sensory Modality Assessment and Rehabilitation Technique (SMART): a behavioral assessment scale for disorders of consciousness Revue Neurologique in press.

Cherry, E.C., 1953. Some experiments on the recognition of speech, with one and two ears. Journal of the Acoustical Society of America 25, 975-979.

Childs, N.L., Mercer, W.N., 1996. Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs [letter; comment]. BMJ 313, 944.

Childs, N.L., Mercer, W.N., Childs, H.W., 1993. Accuracy of diagnosis of persistent vegetative state. Neurology 43, 1465-1467.

Choe, B.Y., Suh, T.S., Choi, K.H., Shinn, K.S., Park, C.K., Kang, J.K., 1995. Neuronal dysfunction in patients with closed head injury evaluated by in vivo 1H magnetic resonance spectroscopy. Invest Radiol 30, 502-506.

Clauss, R., Nel, W., 2006. Drug induced arousal from the permanent vegetative state. NeuroRehabilitation 21, 23-28.

Coleman, M.R., Davis, M.H., Rodd, J.M., Robson, T., Ali, A., Owen, A.M., Pickard, J.D., 2009. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 132, 2541-2552.

Coleman, M.R., Rodd, J.M., Davis, M.H., Johnsrude, I.S., Menon, D.K., Pickard, J.D., Owen, A.M., 2007. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain 130, 2494-2507.

Cordes, D., Haughton, V.M., Arfanakis, K., Wendt, G.J., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2000. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 21, 1636-1644.

Damasio, A., Meyer, K., 2009. Consciousness: An overview of the phenomenon and of its possible neural basis. In: Steven, L., Tononi, G. (Eds.), The neurology of consciousness: Cogntive neuroscience and neuropathology. Academic Press, Oxford, UK, pp. 3-14.

Connolly, J.F., Stewart, S.H., Phillips, N.A., 1990. The effects of processing requirements on neurophysiological responses to spoken sentences. Brain Lang 39, 302-318.

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103, 13848-13853.

De Giorgio, C.M., Rabinowicz, A.L., Gott, P.S., 1993. Predictive value of P300 event-related potentials compared with EEG and somatosensory evoked potentials in non-traumatic coma. Acta Neurol Scand 87, 423-427.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., Smith, S.M., 2006. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29, 1359-1367.

De Tiege, X., Bier, J.C., Massat, I., Laureys, S., Lotstra, F., Berre, J., Mendlewicz, J., Goldman, S., 2003. Regional cerebral glucose metabolism in akinetic catatonia and after remission. J Neurol Neurosurg Psychiatry 74, 1003-1004.

Dehaene, S., Changeux, J.P., 2005. Ongoing spontaneous activity controls access to consciousness: a neuronal model for inattentional blindness. PLoS Biol 3, e141.

Demertzi, A., Vanhaudenhuyse, A., Bruno, M.A., Schnakers, C., Boly, M., Boveroux, P., Maquet, P., Moonen, G., Laureys, S., 2008. Is there anybody in there? Detecting awareness in disorders of consciousness. Expert Rev Neurother 8, 1719-1730.

Devue, C., Bredart, S., 2008. Attention to self-referential stimuli: can I ignore my own face? Acta Psychol (Amst) 128, 290-297.

Devue, C., Van der Stigchel, S., Bredart, S., Theeuwes, J., 2009. You do not find your own face faster; you just look at it longer. Cognition 111, 114-122.

Di, H., Boly, M., Weng, X., Ledoux, D., Laureys, S., 2008. Neuroimaging activation studies in the vegetative state: predictors of recovery? Clin Med 8, 502-507.

Di, H.B., Yu, S.M., Weng, X.C., Laureys, S., Yu, D., Li, J.Q., Qin, P.M., Zhu, Y.H., Zhang, S.Z., Chen, Y.Z., 2007. Cerebral response to patient's own name in the vegetative and minimally conscious states. Neurology 68, 895-899.

Drevets, W.C., Burton, H., Videen, T.O., Snyder, A.Z., Simpson, J.R., Jr., Raichle, M.E., 1995. Blood flow changes in human somatosensory cortex during anticipated stimulation. Nature 373, 249-252.

Fernandez-Espejo, D., Junque, C., Vendrell, P., Bernabeu, M., Roig, T., Bargallo, N., Mercader, J.M., 2008. Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. Brain Inj 22, 882-890.

Filippi, C.G., Ulug, A.M., Ryan, E., Ferrando, S.J., van Gorp, W., 2001. Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. AJNR Am J Neuroradiol 22, 277-283.

Fins, J., 2007. Ethics of CLinical decision making and communication surrogates. . In: Posner, J.B., Saper, C., Schiff, N., Plum, F. (Eds.), Plum and Posner's diagnosis of stupor and coma. Oxford University Press, pp. 376-380.

Fins, J., 2009. Neuroethics and Disorders of Consciousness: A Pragmatic Approach to Neuropalliative Care. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. . Elsevier, Oxford, pp. 234-246.

Fischer, C., Ibanez, V., Jourdan, C., Grau, A., Mauguiere, F., Artru, F., 1988. [Early and middle latency auditory evoked potentials and somatosensory evoked potentials in the vital and functional prognosis of severe brain injuries in intensive care]. Agressologie 29, 359-363.

Fischer, C., Luaute, J., Adeleine, P., 2004. Predictive value of sensory and cognitive evoked potentials for awakening from coma. Neurology 63, 669-673.

Fischer, C., Luaute, J., Nemoz, C., Morlet, D., Kirkorian, G., Mauguiere, F., 2006. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Crit Care Med 34, 1520-1524.

Fischer, C., Luaute, J., Salord, F., Jourdan, C., Morlet, D., 2001. Valeur pronostique des PEA au stade aigu du coma. PE auditifs precoces, de latence moyenne, tardifs et negativite de discordance (MMN). In: Guerit, J. (Ed.), L’evaluation neurophysiologique des comas, de la mort encephalique et des etats vegetatifs. Solal, Marseille, pp. 169-181.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences 102, 9673-9678.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8, 700-711.

Fransson, P., 2005. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26, 15-29.

Fransson, P., Marrelec, G., 2008. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage 42, 1178-1184.

Friedman, S.D., Brooks, W.M., Jung, R.E., Chiulli, S.J., Sloan, J.H., Montoya, B.T., Hart, B.L., Yeo, R.A., 1999. Quantitative proton MRS predicts outcome after traumatic brain injury. Neurology 52, 1384-1391.

Fuhrmann Alpert, G., Hein, G., Tsai, N., Naumer, M.J., Knight, R.T., 2008. Temporal characteristics of audiovisual information processing. J Neurosci 28, 5344-5349.

Fukuda, K., 1994. Analysis of eyeblink activity during discriminative tasks. Percept Mot Skills 79, 1599-1608.

Gallup, G.G., 1970. Chimpanzees: Self-recognition. Science 167, 86-87.

Gallup, G.G., 1979. Self-awareness in primates. American Scientist 67, 417–421.

Garcia-Larrea, L., Artru, F., Bertrand, O., Pernier, J., Mauguiere, F., 1992. The combined monitoring of brain stem auditory evoked potentials and intracranial pressure in coma. A study of 57 patients. J Neurol Neurosurg Psychiatry 55, 792-798.

Garnett, M.R., Blamire, A.M., Corkill, R.G., Cadoux-Hudson, T.A., Rajagopalan, B., Styles, P., 2000. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. Brain 123 (Pt 10), 2046-2054.

Gawryluk, J.R., D'Arcy, R.C., Connolly, J.F., Weaver, D.F., 2010. Improving the clinical assessment of consciousness with advances in electrophysiological and neuroimaging techniques. BMC Neurol 10, 11.

Giacino, J.T., 1997. Disorders of consciousness: differential diagnosis and neuropathologic features. Semin. Neurol. 17, 105-111.

Giacino, J.T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D.I., Kelly, J.P., Rosenberg, J.H., Whyte, J., Zafonte, R.D., Zasler, N.D., 2002. The minimally conscious state: Definition and diagnostic criteria. Neurology 58, 349-353.

Giacino, J.T., Kalmar, K., 1997. The vegetative and minimally conscious states: A comparison of clinical features and functional outcome. J Head Trauma Rehabil 12, 36-51.

Giacino, J.T., Kalmar, K., Whyte, J., 2004. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85, 2020-2029.

Gill-Thwaites, H., 2006. Lotteries, loopholes and luck: misdiagnosis in the vegetative state patient. Brain Inj 20, 1321-1328.

Gill-Thwaites, H., Munday, R., 2004. The sensory modality assessment and rehabilitation technique (SMART): a valid and reliable assessment for vegetative state and minimally conscious state patients. Brain Inj 18, 1255-1269.

Gillihan, S.J., Farah, M.J., 2005. Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. Psychol Bull 131, 76-97.

Giorgianni, R., Lo Presti, R., D'Aleo, G., Mondo, N., Di Bella, P., Bramanti, P., 1997. Event-related potentials in patients in persistent vegetative state. EEG Journal 103, 149.

Glass, I., Sazbon, L., Groswasser, Z., 1998. Mapping "cognitive" event-related potentials in prolonged postcoma unawareness state. Clin Electroencephalogr 29, 19-30.

Goldberg, II, Harel, M., Malach, R., 2006. When the brain loses its self: prefrontal inactivation during sensorimotor processing. Neuron 50, 329-339.

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., Hasson, U., Malach, R., 2007. Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. Cereb Cortex 17, 766-777.

Gosseries, O., Bruno, M.-A., vanhaudenhuyse, A., Laureys, S., Schnakers, C., 2009. Consciousness in the Locked-in Syndrome. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. Elsevier, Oxford, pp. 191-203.

Gott, P.S., Rabinovicz, A.L., DiGiorgio, C.M., 1991. P300 auditory event-related potentials in nontraumatic coma: association with Glasgow Coma Score and awakening. Arch Neurol 48, 1267-1270.

Greenberg, D.L., 2007. Comment on "Detecting awareness in the vegetative state". Science 315, 1221; author reply 1221.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 62, 429-437.

Greicius, M.D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A.L., Menon, V., 2008. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp 29, 839-847.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 101, 4637-4642.

Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19, 72-78.

Gronau, N., Cohen, A., Ben-Shakhar, G., 2003. Dissociations of personally significant and task-relevant distractors inside and outside the focus of attention: a combined behavioral and psychophysiological study. J Exp Psychol Gen 132, 512-529.

Guerit, J.M., Verougstraete, D., de Tourtchaninoff, M., Debatisse, D., Witdoeckt, C., 1999. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. Clin Neurophysiol 110, 1260-1269.

Guerit, J.M., Verougstraete, D., de Tourtchaninoff, M., Debatisse, D., Witdoeckt, C., 1999. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. Clin Neurophysiol 110, 1260-1269.

Gusnard, D.A., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2, 685-694.

Gutling, E., Isenmann, S., Wichmann, W., 1996. Electrophysiology in the locked-in-syndrome. Neurology 46, 1092-1101.

Hackley, S.A., Johnson, L.N., 1996. Distinct early and late subcomponents of the photic blink reflex: response characteristics in patients with retrogeniculate lesions. Psychophysiology 33, 239-251.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol 6, e159.

Hagoort, P., Brown, C.M., Swaab, T.Y., 1996. Lexical-semantic event-related potential effects in patients with left hemisphere lesions and aphasia, and patients with right hemisphere lesions without aphasia. Brain 119 (Pt 2), 627-649.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Liegeois, C., Chauvel, P., Musolino, A., 1995. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr Clin Neurophysiol 94, 191-220.

Hall, A., 1945. The Origin and Purposes of Blinking. Br J Ophthalmol 29, 445-467.

Harris, D.P., Hall, J.W., 3rd, 1990. Feasibility of auditory event-related potential measurement in brain injury rehabilitation. Ear Hear 11, 340-350.

Hauk, O., Johnsrude, I., Pulvermuller, F., 2004. Somatotopic representation of action words in human motor and premotor cortex. Neuron 41, 301-307.

Hillyard, S.A., Hink, R.F., Schwent, V.L., Picton, T.W., 1973. Electrical signs of selective attention in the human brain. Science 182, 177-180.

Hinterberger, T., Wilhelm, B., Mellinger, J., Kotchoubey, B., Birbaumer, N., 2005. A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients. IEEE Trans Biomed Eng 52, 211-220.

Horovitz, S.G., Braun, A.R., Carr, W.S., Picchioni, D., Balkin, T.J., Fukunaga, M., Duyn, J.H., 2009. Decoupling of the brain's default mode network during deep sleep. Proc Natl Acad Sci U S A 106, 11376-11381.

Horovitz, S.G., Fukunaga, M., de Zwart, J.A., van Gelderen, P., Fulton, S.C., Balkin, T.J., Duyn, J.H., 2008. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. Hum Brain Mapp 29, 671-682.

Houlden, D.A., Taylor, A.B., Feinstein, A., Midha, R., Bethune, A.J., Stewart, C.P., Schwartz, M.L., 2010. Early somatosensory evoked potential grades in comatose traumatic brain injury patients predict cognitive and functional outcome. Crit Care Med 38, 167-174.

Huisman, T.A., Loenneker, T., Barta, G., Bellemann, M.E., Hennig, J., Fischer, J.E., Il'yasov, K.A., 2006. Quantitative diffusion tensor MR imaging of the brain: field strength related variance of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) scalars. Eur Radiol 16, 1651-1658.

Huisman, T.A., Schwamm, L.H., Schaefer, P.W., Koroshetz, W.J., Shetty-Alva, N., Ozsunar, Y., Wu, O., Sorensen, A.G., 2004. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am J Neuroradiol 25, 370-376.

Huisman, T.A., Sorensen, A.G., Hergan, K., Gonzalez, R.G., Schaefer, P.W., 2003. Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. J Comput Assist Tomogr 27, 5-11.

Jacome, D.E., Morilla-Pastor, D., 1990. Unreactive EEG: pattern in locked-in syndrome. Clin Electroencephalogr 21, 31-36.

Jagger, J., Jane, J.A., Rimel, R., 1983. The Glasgow coma scale: to sum or not to sum? Lancet 2, 97.

James, W., 1890. The Principles of Psychology. Macmillan Publishing Co Inc, New York.

Jennett, B., 2002. The vegetative state. J Neurol Neurosurg Psychiatry 73, 355-357.

Jennett, B., 2005. The assessment and rehabilitation of vegetative and minimally conscious patients: Definitions, diagnosis, prevalence and ethics. Neuropsychol Rehabil 15, 163-165.

Jennett, B., Cranford, R., Zasler, N., 1997. Consensus statement on criteria for the persistent vegetative state is being developed [letter]. BMJ 314, 1621-1622.

Jennett, B., Plum, F., 1972. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet 1, 734-737.

Jones, D.K., Dardis, R., Ervine, M., Horsfield, M.A., Jeffree, M., Simmons, A., Jarosz, J., Strong, A.J., 2000. Cluster analysis of diffusion tensor magnetic resonance images in human head injury. Neurosurgery 47, 306-313; discussion 313-304.

Jorgensen, E.O., 1973. Spinal man after brain death. The unilateral extension-pronation reflex of the upper limb as an indication of brain death. Acta Neurochir (Wien) 28, 259-273.

Kaisti, K.K., Langsjo, J.W., Aalto, S., Oikonen, V., Sipila, H., Teras, M., Hinkka, S., Metsahonkala, L., Scheinin, H., 2003. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99, 603-613.

Kampfl, A., Schmutzhard, E., Franz, G., Pfausler, B., Haring, H.P., Ulmer, H., Felber, S., Golaszewski, S., Aichner, F., 1998. Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. Lancet 351, 1763-1767.

Kane, N.M., Curry, S.H., Butler, S.R., Cummins, B.H., 1993. Electrophysiological indicator of awakening from coma. Lancet 341, 688.

Kane, N.M., Curry, S.H., Rowlands, C.A., Manara, A.R., Lewis, T., Moss, T., Cummins, B.H., Butler, S.R., 1996. Event-related potentials--neurophysiological tools for predicting emergence and early outcome from traumatic coma. Intensive Care Med 22, 39-46.

Keane, J.R., 1985. Locked-in syndrome with deafness. Neurology 35, 1395.

Kircher, T.T., Senior, C., Phillips, M.L., Benson, P.J., Bullmore, E.T., Brammer, M., Simmons, A., Williams, S.C., Bartels, M., David, A.S., 2000. Towards a functional neuroanatomy of self processing: effects of faces and words. Cogn Brain Res 10, 133-144.

Kircher, T.T., Senior, C., Phillips, M.L., Rabe-Hesketh, S., Benson, P.J., Bullmore, E.T., Brammer, M., Simmons, A., Bartels, M., David, A.S., 2001. Recognizing one's own face. Cognition 78, B1-B15.

Knauff, M., Fangmeier, T., Ruff, C.C., Johnson-Laird, P.N., 2003. Reasoning, models, and images: behavioral measures and cortical activity. J Cogn Neurosci 15, 559-573.

Kotchoubey, B., Lang, S., 2001. Event-related potentials in an auditory semantic oddball task in humans. Neurosci Lett 310, 93-96.

Kotchoubey, B., Lang, S., Bostanov, V., Birbaumer, N., 2002. Is there a Mind? Electrophysiology of Unconscious Patients. News Physiol Sci 17, 38-42.

Kotchoubey, B., Lang, S., Herb, E., Maurer, P., Schmalohr, D., Bostanov, V., Birbaumer, N., 2003. Stimulus complexity enhances auditory discrimination in patients with extremely severe brain injuries. Neurosci Lett 352, 129-132.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., Bostanov, V., Birbaumer, N., 2005. Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. Clinical Neurophysiology 116, 2441-2453.

Kübler, A., 2009. Brain-Computer Interfaces for Communication in Paralysed Patients and Implications for Disorders of Consciousness. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. Elsevier, Oxford, pp. 217-233.

Kubler, A., Neumann, N., 2005. Brain-computer interfaces - the key for the conscious brain locked into a paralyzed body. Prog Brain Res 150, 513-525.

Kutas, M., Hillyard, S., 1989. An electrophysiological probe of incidental semantic association. J Cogn Neurosci 1, 38-49.

Kutas, M., Hillyard, S.A., 1980. Event-related brain potentials to semantically inappropriate and surprisingly large words. Biol Psychol 11, 99-116.

Laureys, S., 2005a. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci 9, 556-559.

Laureys, S., 2005b. Science and society: death, unconsciousness and the brain. Nat Rev Neurosci 6, 899-909.

Laureys, S., Bruno, M.-A., Schnakers, C., Gosseries, O., 2010. Réseau de soins adapté pour les patients comateux - rapports 2007-2010. SPF santé publique.

Laureys, S., Boly, M., Moonen, G., Maquet, P., 2008. Arousal and awareness in coma and post-comatose states. In: Squire, L. (Ed.), New Encyclopedia of Neuroscience. Eslevier.

Laureys, S., Faymonville, M.E., Berre, J., 2000a. Permanent vegetative state and persistent vegetative state are not interchangeable terms. BMJ 321, 916.

Laureys, S., Faymonville, M.E., Degueldre, C., Fiore, G.D., Damas, P., Lambermont, B., Janssens, N., Aerts, J., Franck, G., Luxen, A., Moonen, G., Lamy, M., Maquet, P., 2000b. Auditory processing in the vegetative state. Brain 123 (Pt 8), 1589-1601.

Laureys, S., Faymonville, M.E., Luxen, A., Lamy, M., Franck, G., Maquet, P., 2000c. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet 355, 1790-1791.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., Franck, G., Maquet, P., 1999a. Impaired effective cortical connectivity in vegetative state. Neuroimage 9, 377-382.

Laureys, S., Lemaire, C., Maquet, P., Phillips, C., Franck, G., 1999b. Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry 67, 121.

Laureys, S., Owen, A.M., Schiff, N.D., 2004a. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 3, 537-546.

Laureys, S., Pellas, F., Van Eeckhout, P., Ghorbel, S., Schnakers, C., Perrin, F., Berre, J., Faymonville, M.E., Pantke, K.H., Damas, F., Lamy, M., Moonen, G., Goldman, S., 2005a. The locked-in syndrome : what is it like to be conscious but paralyzed and voiceless? Prog Brain Res 150, 495-511.

Laureys, S., Perrin, F., Bredart, S., 2007. Self-consciousness in non-communicative patients. Conscious Cogn 16, 722-741.

Laureys, S., Perrin, F., Faymonville, M.E., Schnakers, C., Boly, M., Bartsch, V., Majerus, S., Moonen, G., Maquet, P., 2004b. Cerebral processing in the minimally conscious state. Neurology 63, 916-918.

Laureys, S., Perrin, F., Schnakers, C., Boly, M., Majerus, S., 2005b. Residual cognitive function in comatose, vegetative and minimally conscious states. Curr Opin Neurol 18, 726-733.

Leon-Carrion, J., van Eeckhout, P., Dominguez-Morales Mdel, R., 2002. The locked-in syndrome: a syndrome looking for a therapy. Brain Inj 16, 555-569.

Levy, D.E., Sidtis, J.J., Rottenberg, D.A., Jarden, J.O., Strother, S.C., Dhawan, V., Ginos, J.Z., Tramo, M.J., Evans, A.C., Plum, F., 1987. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann Neurol 22, 673-682.

Lew HL, D.S., Slimp J, et al., 2003. Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. Am J Phys Med Rehabil 82, 53-61.

Lew, H.L., Slimp, J., Price, R., Massagli, T.L., Robinson, L.R., 1999. Comparison of speech-evoked v tone-evoked P300 response: implications for predicting outcomes in patients with traumatic brain injury. Am J Phys Med Rehabil 78, 367-371.

Lieberman, M.D., 2007. Social cognitive neuroscience: a review of core processes. Annu Rev Psychol 58, 259-289.

Liegeois-Chauvel, C., de Graaf, J.B., Laguitton, V., Chauvel, P., 1999. Specialization of left auditory cortex for speech perception in man depends on temporal coding [In Process Citation]. Cereb Cortex 9, 484-496.

Litscher, G., Schwarz, G., Kleinert, R., 1995. Brain-stem auditory evoked potential monitoring. Variations of stimulus artifact in brain death. Electroencephalogr Clin Neurophysiol 96, 413-419.

Liu, G.T., Ronthal, M., 1992. Reflex blink to visual threat. J Clin Neuroophthalmol 12, 47-56.

Logi, F., Fischer, C., Murri, L., Mauguiere, F., 2003. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 114, 1615-1627.

Lombardi, F., Taricco, M., De Tanti, A., Telaro, E., Liberati, A., 2002. Sensory stimulation of brain-injured individuals in coma or vegetative state: results of a Cochrane systematic review. Clin Rehabil 16, 464-472.

Lou, H.C., Luber, B., Crupain, M., Keenan, J.P., Nowak, M., Kjaer, T.W., Sackeim, H.A., Lisanby, S.H., 2004. Parietal cortex and representation of the mental Self. Proceedings of the National Academy of Sciences 101, 6827-6832.

Majerus, S., Bruno, M.A., Schnakers, C., Giacino, J.T., Laureys, S., 2009. The problem of aphasia in the assessment of consciousness in brain-damaged patients. Prog Brain Res 177, 49-61.

Majerus, S., Gill-Thwaites, H., Andrews, K., Laureys, S., 2005. Behavioral evaluation of consciousness in severe brain damage. Prog Brain Res 150, 397-413.

Mans, L., Cicchetti, D., Sroufe, L.A., 1978. Mirrow reactions of Down's syndrome infants and toddlers: cognitive underpinnings of self-recognition. Child Dev 49, 1247-1250.

Maquet, P., Dive, D., Salmon, E., Sadzot, B., Franco, G., Poirrier, R., von, Frenckell, R., Franck, G., 1990. Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. Brain Res. 513, 136-143.

Maquet, P., Ruby, P., Maudoux, A., Albouy, G., Sterpenich, V., Dang-Vu, T., Desseilles, M., Boly, M., Perrin, F., Peigneux, P., Laureys, S., 2005. Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 150, 219-227.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315, 393-395.

Markand, O.N., 1976. Electroencephalogram in "locked-in" syndrome. Electroencephalogr Clin Neurophysiol 40, 529-534.

Marosi, M., Prevec, T., Masala, C., Bramanti, P., Giorganni, R., Luef, G., Berek, K., Saltuari, L., Bramanti, M., 1993. Event-related potentials in vegetative state [letter; comment] [published erratum appears in Lancet 1993 Nov 13;342(8881):1248]. Lancet 341, 1473.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., Crivello, F., Joliot, M., Petit, L., Tzourio-Mazoyer, N., 2001. Cortical networks for working memory and executive functions sustain the conscious resting state in man. Brain Res Bull 54, 287-298.

Mazzini, L., Zaccala, M., Gareri, F., Giordano, A., Angelino, E., 2001. Long-latency auditory-evoked potentials in severe traumatic brain injury. Arch Phys Med Rehabil 82, 57-65.

McCarthy, G., Nobre, A.C., Bentin, S., Spencer, D.D., 1995. Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. J Neurosci 15, 1080-1089.

McKiernan, K.A., D'Angelo, B.R., Kaufman, J.N., Binder, J.R., 2006. Interrupting the "stream of consciousness": an fMRI investigation. Neuroimage 29, 1185-1191.

McQuillen, M.P., 1991. Can people who are unconscious or in the "vegetative state" perceive pain? Issues Law Med. 6, 373-383.

Menon, D.K., Owen, A.M., Williams, E.J., Minhas, P.S., Allen, C.M., Boniface, S.J., Pickard, J.D., 1998. Cortical processing in persistent vegetative state. Lancet 352, 200.

Mollaret, P., Goulon, M., 1959. Le coma dépassé. Rev Neurol 101, 3-15.

Monti, M.M., Coleman, M.R., Owen, A.M., 2009. Neuroimaging and the vegetative state: resolving the behavioral assessment dilemma? Ann N Y Acad Sci 1157, 81-89.

Monti, M. & Vanhaudenhuyse, A., Coleman, M., Boly, M., Pickard, J., Tshibanda, L., Owen, A., Laureys, S., 2010. Willful modulation of brain activity and communication in disorders of consciousness. New England Journal of Medicine in press.

Moray, N., 1959. Attention in dichotic listening: affective cues and the influence of instructions. Q J Exp Psychol 11, 56-60.

Morcom, A.M., Fletcher, P.C., 2007. Does the brain have a baseline? Why we should be resisting a rest. Neuroimage 37, 1073-1082.

Morita, T., Itakura, S., Saito, D.N., Nakashita, S., Harada, T., Kochiyama, T., Sadato, N., 2008. The role of the right prefrontal cortex in self-evaluation of the face: a functional magnetic resonance imaging study. J Cogn Neurosci 20, 342-355.

Moskopp, D., Stahle, C., Wassmann, H., 1995. Problems of the Glasgow Coma Scale with early intubated patients. Neurosurg Rev 18, 253-257.

Murray, G.D., Teasdale, G.M., Braakman, R., Cohadon, F., Dearden, M., Iannotti, F., Karimi, A., Lapierre, F., Maas, A., Ohman, J., Persson, L., Servadei, F., Stocchetti, N., Trojanowski, T., Unterberg, A., 1999. The European Brain Injury Consortium survey of head injuries. Acta Neurochir (Wien) 141, 223-236.

Mutschler, V., Chaumeil, C.G., Marcoux, L., Wioland, N., Tempe, J.D., Kurtz, D., 1996. Auditory P300 in subjects in a post-anoxic coma. Preliminary data. Neurophysiologie Clinique 26, 158-163.

Naatanen, R., Gaillard, A.W., Mantysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst) 42, 313-329.

Naatanen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., Vainio, M., Alku, P., Ilmoniemi, R.J., Luuk, A., Allik, J., Sinkkonen, J., Alho, K., 1997. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature 385, 432-434.

Naatanen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24, 375-425.

Naccache, L., Puybasset, L., Gaillard, R., Serve, E., Willer, J.C., 2005. Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure. Clin Neurophysiol 116, 988-989.

Nachev, P., Husain, M., 2007. Comment on "Detecting awareness in the vegetative state". Science 315, 1221; author reply 1221.

Nakayama, N., Okumura, A., Shinoda, J., Nakashima, T., Iwama, T., 2006. 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 77, 856-862.

Neuman, C.J., Hill, S.D., 1978. Self-recognition and stimulus preference in autistic children. Dev Psychobiol 11, 571-578.

Nielsen, M., Suddendorf, T., Slaughter, V., 2006. Mirror self-recognition beyond the face. Child Dev 77, 176-185.

Olichney, J., Pratt, H., Starr, A., 1993. Blinking in patients with memory disorders during short term memory tasks. Int J Neurosci 70, 169-180.

Orchard, L.N., Stern, J.A., 1991. Blinks as an index of cognitive activity during reading. Integr Physiol Behav Sci 26, 108-116.

Owen, A., Coleman, M., Boly, M., Davis, M., Laureys, S., Jolles, J., Pickard, J., 2007. Response to Comments on "Detecting Awareness in the Vegetative State". Science 315

Owen, A., Schiff, N.D., Laureys, S., 2009. The Assessment of Conscious Awareness in the Vegetative State. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Counsciousness: Cognitive Neuroscience and Neuropathology. Elsevier, Oxford, pp. 163-190.

Owen, A.M., Coleman, M.R., 2008. Functional neuroimaging of the vegetative state. Nat Rev Neurosci 9, 235-243.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard, J.D., 2006. Detecting awareness in the vegetative state. Science 313, 1402.

Owen, A.M., Menon, D.K., Johnsrude, I.S., Bor, D., Scott, S.K., Manly, T., Williams, E.J., Mummery, C., Pickard, J.D., 2002. Detecting residual cognitive function in persistent vegetative state. Neurocase 8, 394-403.

Passler, M.A., Riggs, R.V., 2001. Positive outcomes in traumatic brain injury-vegetative state: patients treated with bromocriptine. Arch Phys Med Rehabil 82, 311-315.

Patterson, J.R., Grabois, M., 1986. Locked-in syndrome: a review of 139 cases. Stroke 17, 758-764.

Perlbarg, V., Puybasset, L., Tollard, E., Lehericy, S., Benali, H., Galanaud, D., 2009. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. Hum Brain Mapp.

Perrin, F., García-Larrea, L., Mauguiere, F., Bastuji, H., 1999. A differential brain response to the subject's own name persists during sleep. Clin Neurophysiol 110, 2153-2164.

Perrin, F., Peigneux, P., Maquet, P., Degueldre, C., Luxen, A., Phillips, C., Aerts, J., Del Fiore, G., Laureys, S., 2003. Neural mechanisms involved in the detection of our given name: A multi-modal study using event-related potentials and positron emission tomography. Eur J Neurology 10 (Suppl. 1), 14-15.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., Faymonville, M.E., Lamy, M., Moonen, G., Luxen, A., Maquet, P., Laureys, S., 2006. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol 63, 562-569.

Picton, T.W., 1992. The P300 wave of the human event-related potential. J Clin Neurophysiol 9, 456-479.

Platek, S.M., Loughead, J.W., Gur, R.C., Busch, S., Ruparel, K., Phend, N., Panyavin, I.S., Langleben, D.D., 2006. Neural substrates for functionally discriminating self-face from personally familiar faces. Hum Brain Mapp 27, 91-98.

Plotnik, J.M., de Waal, F.B., Reiss, D., 2006. Self-recognition in an Asian elephant. Proc Natl Acad Sci U S A 103, 17053-17057.

Plum, F., Posner, J.B., 1966. The diagnosis of stupor and coma., 1st ed. Davis, F.A., Philadelphia.

Posner, J., Saper, C., Schiff, N., Plum, F., 2007. Plum and Posner's diagnosis of stupor and coma. Oxford University Press, New York.

Prevec, T., Saltuari, L., Masala, C., 1993. Mental functions in apallic patients after traumatic cerebral lesions. Electroencephalogr Clin Neurophysiol 87.

Priel, B., de Schonen, S., 1986. Self-recognition: a study of a population without mirrors. J Exp Child Psychol 41, 237-250.

Rademaker, G.G., Garcin, J., 1934. The threat blink-reflex. L'Encéphale 29.

Raichle, M.E., 2006. Neuroscience. The brain's dark energy. Science 314, 1249-1250.

Rappaport, M., McCandless, K., Pond W, Krafft MC, 1991. Passive P300 response in traumatic brain injury patients. J Neuropsychiatry Clin Neurosci 3, 180-185.

Rees, G., 2007. Neural correlates of the contents of visual awareness in humans. Philos Trans R Soc Lond B Biol Sci. 362, 877-886.

Reiss, D., Marino, L., 2001. Mirror self-recognition in the bottlenose dolphin: a case of cognitive convergence. Proc Natl Acad Sci U S A 98, 5937-5942.

Ricci, R., Barbarella, G., Musi, P., Boldrini, P., Trevisan, C., Basaglia, N., 1997. Localised proton MR spectroscopy of brain metabolism changes in vegetative patients. Neuroradiology, 313-319.

Robinson, L.R., Micklesen, P.J., Tirschwell, D.L., Lew, H.L., 2003. Predictive value of somatosensory evoked potentials for awakening from coma. Crit Care Med 31, 960-967.

Rochat, P., Striano, T., 2002. Who's in the mirror? Self-other discrimination in specular images by four- and nine-month-old infants. Child Dev 73, 35-46.

Ross, B.D., Ernst, T., Kreis, R., Haseler, L.J., Bayer, S., Danielsen, E., Bluml, S., Shonk, T., Mandigo, J.C., Caton, W., Clark, C., Jensen, S.W., Lehman, N.L., Arcinue, E., Pudenz, R., Shelden, C.H., 1998. 1H MRS in acute traumatic brain injury. J Magn Reson Imaging 8, 829-840.

Rowley, G., Fielding, K., 1991. Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users. Lancet 337, 535-538.

Royal College of Physicians, 2003. The vegetative state: guidance on diagnosis and management. Clin Med 3, 249-254.

Sadleir, L.G., Scheffer, I.E., Smith, S., Connolly, M.B., Farrell, K., 2009. Automatisms in absence seizures in children with idiopathic generalized epilepsy. Arch Neurol 66, 729-734.

Sanchez-Pena, P., Pereira, A.R., Sourour, N.A., Biondi, A., Lejean, L., Colonne, C., Boch, A.L., Al Hawari, M., Abdennour, L., Puybasset, L., 2008. S100B as an additional prognostic marker in subarachnoid aneurysmal hemorrhage. Crit Care Med 36, 2267-2273.

Saposnik, G., Bueri, J.A., Maurino, J., Saizar, R., Garretto, N.S., 2000. Spontaneous and reflex movements in brain death. Neurology 54, 221-223.

Saposnik, G., Maurino, J., Saizar, R., Bueri, J.A., 2005. Spontaneous and reflex movements in 107 patients with brain death. Am J Med 118, 311-314.

Sawyer, E., Mauro, L.S., Ohlinger, M.J., 2008. Amantadine enhancement of arousal and cognition after traumatic brain injury. Ann Pharmacother 42, 247-252.

Scherg, M., Von Cramon, D., 1985. Two bilateral sources of the late AEP as identified by a spatio-temporal dipole model. Electroencephalogr Clin Neurophysiol 62, 32-44.

Schiff, N.D., Fins, J.J., 2007. Deep brain stimulation and cognition: moving from animal to patient. Curr Opin Neurol 20, 638-642.

Schiff, N.D., Giacino, J.T., Kalmar, K., Victor, J.D., Baker, K., Gerber, M., Fritz, B., Eisenberg, B., Biondi, T., O'Connor, J., Kobylarz, E.J., Farris, S., Machado, A., McCagg, C., Plum, F., Fins, J.J., Rezai, A.R., 2007. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 448, 600-603.

Schiff, N.D., Rodriguez-Moreno, D., Kamal, A., Kim, K.H., Giacino, J.T., Plum, F., Hirsch, J., 2005. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 64, 514-523.

Schnakers, C., Chatelle, C., Vanhaudenhuyse, A., Majerus, S., Ledoux, D., Boly, M., Bruno, M.A., Boveroux, P., Demertzi, A., Moonen, G., Laureys, S., 2010. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Pain 148, 215-219.

Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., Malone, R., Laureys, S., 2006. Does the FOUR score correctly diagnose the vegetative and minimally conscious states? Ann Neurol 60, 744-745.

Schnakers, C., Hustinx, R., Vandewalle, G., Majerus, S., Moonen, G., Boly, M., Vanhaudenhuyse, A., Laureys, S., 2008a. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry 79, 225-227.

Schnakers, C., Majerus, S., Giacino, J., Vanhaudenhuyse, A., Bruno, M.-A., Boly, M., Moonen, G., Damas, P., Lambermont, B., Lamy, M., Damas, F.o., Ventura, M., Laureys, S., 2008b. A French validation study of the Coma Recovery Scale-Revised (CRS-R). Brain Injury 22, 786 - 792.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., Pellas, F., Bartsch, V., Peigneux, P., Moonen, G., Laureys, S., 2008c. Cognitive function in the locked-in syndrome. J Neurol 255, 323-330.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., Boly, M., Vanhaudenhuyse, A., Bruno, M.A., Laureys, S., 2009a. Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. Neurocase, 1-7.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., Boly, M., Vanhaudenhuyse, A., Bruno, M.A., Moonen, G., Laureys, S., 2008d. Voluntary brain processing in disorders of consciousness. Neurology 71, 1614-1620.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., Moonen, G., Laureys, S., 2009b. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 9, 35.

Schnakers, C., Zasler, N.D., 2007. Pain assessment and management in disorders of consciousness. Curr Opin Neurol 20, 620-626.

Schoenle, P.W., Witzke, W., 2004. How vegetative is the vegetative state? Preserved semantic processing in VS patients--evidence from N 400 event-related potentials. NeuroRehabilitation 19, 329-334.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27, 2349-2356.

Shanmuganathan, K., Gullapalli, R.P., Mirvis, S.E., Roys, S., Murthy, P., 2004. Whole-brain apparent diffusion coefficient in traumatic brain injury: correlation with Glasgow Coma Scale score. AJNR Am J Neuroradiol 25, 539-544.

Shehzad, Z., Kelly, A.M., Reiss, P.T., Gee, D.G., Gotimer, K., Uddin, L.Q., Lee, S.H., Margulies, D.S., Roy, A.K., Biswal, B.B., Petkova, E., Castellanos, F.X., Milham, M.P., 2009. The resting brain: unconstrained yet reliable. Cereb Cortex 19, 2209-2229.

Shiel, A., Horn, S.A., Wilson, B.A., Watson, M.J., Campbell, M.J., McLellan, D.L., 2000. 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 14, 408-416.

Shulman, G.L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M., Petersen, S.E., 1997a. Top-down modulation of early sensory cortex. Cereb Cortex 7, 193-206.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E., 1997b. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci. 9, 648-663.

Signorino, M., D'Acunto, S., Angeleri, F., Pietropaoli, P., 1995. Eliciting P300 in comatose patients. Lancet 345, 255-256.

Signorino, M., D'Acunto, S., Cercaci, S., Pietropaoli, P., Angeleri, F., 1997. The P300 in traumatic coma: Conditioning of the odd-ball paradigm. Journal of Psychophysiology 11, 59-70.

Sinson, G., Bagley, L.J., Cecil, K.M., Torchia, M., McGowan, J.C., Lenkinski, R.E., McIntosh, T.K., Grossman, R.I., 2001. Magnetization Transfer Imaging and Proton MR Spectroscopy in the Evaluation of Axonal Injury: Correlation with Clinical Outcome after Traumatic Brain Injury. AJNR Am J Neuroradiol 22, 143-123.

Smart, C.M., Giacino, J.T., Cullen, T., Moreno, D.R., Hirsch, J., Schiff, N.D., Gizzi, M., 2008. A case of locked-in syndrome complicated by central deafness. Nat Clin Pract Neurol 4, 448-453.

Smith, M.E., Stapleton, J.M., Halgren, E., 1986. Human medial temporal lobe potentials evoked in memory and language tasks. Electroencephalogr Clin Neurophysiol 63, 145-159.

Soddu, A., Vanhaudenhuyse, A., Demertzi, A., Bruno, M.A., Tshibanda, L., Di, H., Boly, M., Laureys, S., Noirhomme, Q., 2010. Resting state activity in patients with disorders of consciousness Frontiers in press.

Squires, N.K., Squires, K.C., Hillyard, S.A., 1975. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 38, 387-401.

Staffen, W., Kronbichler, M., Aichhorn, M., Mair, A., Ladurner, G., 2006. Selective brain activity in response to one's own name in the persistent vegetative state. J Neurol Neurosurg Psychiatry 77, 1383-1384.

Steriade, M., 1996. Arousal: revisiting the reticular activating system. Science 272, 225-226.

Sugiura, M., Watanabe, J., Maeda, Y., Matsue, Y., Fukuda, H., Kawashima, R., 2005. Cortical mechanisms of visual self-recognition. Neuroimage 24, 143-149.

Suppiej, A., Cappellari, A., Cogo, P.E., 2009. Prognostic role of somatosensory and auditory evoked potentials in paediatric hypoxic-ischemic encephalopathy managed with hypothermia: an illustrative case. Neurophysiol Clin 39, 101-105.

Sutton, S., Braren, M., Zubin, J., John, E.R., 1965. Evoked-potential correlates of stimulus uncertainty. Science 150, 1187-1188.

Taira, T., 2009. Intrathecal administration of GABA agonists in the vegetative state. Prog Brain Res 177, 317-328.

Tavalaro, J., Tayson, R., 1997. Look up for yes. Kodansha America, Inc., New York, NY.

Teasdale, G., Jennett, B., 1974. Assessment of coma and impaired consciousness. A practical scale. Lancet 2, 81-84.

The Multi-Society Task Force on PVS, 1994. Medical aspects of the persistent vegetative state (1). N Engl J Med 330, 1499-1508.

The Quality Standards Subcommittee of the American Academy of Neurology, 1995. Practice parameters: assessment and management of patients in the persistent vegetative state (summary statement). Neurology 45, 1015-1018.

Tian, L., Jiang, T., Liu, Y., Yu, C., Wang, K., Zhou, Y., Song, M., Li, K., 2007. The relationship within and between the extrinsic and intrinsic systems indicated by resting state correlational patterns of sensory cortices. Neuroimage 36, 684-690.

Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., Cozzone, P., Lehericy, S., Chiras, J., Puybasset, L., 2009. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. Crit Care Med 37, 1448-1455.

Tong, F., Nakayama, K., 1999. Robust representations for faces: Evidence from visual search. Journal of Experimental Psychology: Human Perception and Performance 25, 1016-1035.

Tshibanda, L. & Vanhaudenhuyse, A., Boly, M., Soddu, A., Bruno, M.A., Moonen, G., Laureys, S., Noirhomme, Q., 2010. Neuroimaging after coma. Neuroradiology 52, 15-24.

Tshibanda, L. & Vanhaudenhuyse, A., Galanaud, D., Boly, M., Laureys, S., Puybasset, L., 2009. Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls. Prog Brain Res 177, 215-229.

Tsubota, K., Kwong, K.K., Lee, T.Y., Nakamura, J., Cheng, H.M., 1999. Functional MRI of brain activation by eye blinking. Exp Eye Res 69, 1-7.

Uddin, L.Q., Kaplan, J.T., Molnar-Szakacs, I., Zaidel, E., Iacoboni, M., 2005. Self-face recognition activates a frontoparietal "mirror" network in the right hemisphere: an event-related fMRI study. Neuroimage 25, 926-935.

University of Pittsburgh Medical Center policy and procedure manual, 1993. Management of terminally ill patients who may become organ donors after death. Kennedy Inst Ethics J 3, A1-15.

Uzan, M., Albayram, S., Dashti, S.G., Aydin, S., Hanci, M., Kuday, C., 2003. Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. J Neurol Neurosurg Psychiatry 74, 33-38.

van Buuren M, Gladwin TE, Zandbelt BB, van den Heuvel M, Ramsey NF, Kahn RS, Vink M. 2009. Cardiorespiratory effects on default-mode network activity as measured with fMRI. Hum Brain Mapp 30(9):3031-42.

Vanhaudenhuyse, A., Boly, M., Laureys, S., 2009a. Vegetative state. Scholarpedia 4, 4163.

Vanhaudenhuyse, A., Bruno, M.-A., Bredart, S., Plenevaux, A., Laureys, S., 2007a. The challenge of disentangling reportability and phenomenal consciousness in post-comatose states. Behav Brain Sci 30, 529-530.

Vanhaudenhuyse, A., Bruno, M.A., Schnakers, C., Boly, M., Boveroux, P., Moonen, G., Perrin, F., Pellas, F., Pantke, K.-H., Laureys, S., 2007b. Locked-in syndrome and disorders of consciousness: how to detect consciousness? In: Pellas, F., Kiefer, C., Weiss, J., Pélissier, J. (Eds.), Eveil de coma et états limites. Etats végétatifs, états pauci-relationnels et locked-in syndrome. Masson, Issy-les-Moulineaux, pp. 109-116.

Vanhaudenhuyse, A., Demertzi, A., Schabus, M., Noirhomme, Q., Bredart, S., Boly, M., Phillips, C., Soddu, A., Luxen, A., Moonen, G., Laureys, S., 2010a. Two distinct neuronal networks mediate the awareness of environment and of self. Journal of Cognitive Neurosciences in press.

Vanhaudenhuyse, A., Giacino, J., Schnakers, C., Kalmar, K., Smart, C., Bruno, M.A., Gosseries, O., Moonen, G., Laureys, S., 2008a. Blink to visual threat does not herald consciousness in the vegetative state. Neurology.

Vanhaudenhuyse, A., Laureys, S., Perrin, F., 2008b. Cognitive event-related potentials in comatose and post-comatose states. Neurocrit Care 8, 262-270.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L.J., Bruno, M.A., Boveroux, P., Schnakers, C., Soddu, A., Perlbarg, V., Ledoux, D., Brichant, J.F., Moonen, G., Maquet, P., Greicius, M.D., Laureys, S., Boly, M., 2010b. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 133, 161-171.

Vanhaudenhuyse, A., Schnakers, C., Boly, M., Perrin, F., Bredart, S., Laureys, S., 2007c. Detecting consciousness in minimally conscious patients. Réanimation 16, 527-532.

Vanhaudenhuyse, A., Schnakers, C., Bredart, S., Laureys, S., 2008c. Assessment of visual pursuit in post-comatose states: use a mirror. J Neurol Neurosurg Psychiatry 79, 223.

Verleger, R., 1988. The true P3 is hard to see: some comments on Kok's (1986) paper on degraded stimuli. Biol Psychol 27, 45-50.

Viggiano, M.P., Mecacci, L., 2000. Identification of Poppelreuter-like pictures as indexed by blinking. Neuropsychologia 38, 1098-1100.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83-86.

Vogt, B.A., Laureys, S., 2005. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. Prog Brain Res 150, 205-217.

Voss, H.U., Uluc, A.M., Dyke, J.P., Watts, R., Kobylarz, E.J., McCandliss, B.D., Heier, L.A., Beattie, B.J., Hamacher, K.A., Vallabhajosula, S., Goldsmith, S.J., Ballon, D., Giacino, J.T., Schiff, N.D., 2006. Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest 116, 2005-2011.

Wade, D.T., Johnston, C., 1999. The permanent vegetative state: practical guidance on diagnosis and management. B.M.J. 319, 841-844.

Weiskopf, N., Mathiak, K., Bock, S.W., Scharnowski, F., Veit, R., Grodd, W., Goebel, R., Birbaumer, N., 2004. Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). IEEE Trans Biomed Eng 51, 966-970.

Weiss, N., Galanaud, D., Carpentier, A., Naccache, L., Puybasset, L., 2007. Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. Crit Care 11, 230.

White, N.S., Alkire, M.T., 2003. Impaired thalamocortical connectivity in humans during general-anesthetic-induced unconsciousness. Neuroimage 19, 402-411.

Whyte, J., Katz, D., Long, D., DiPasquale, M.C., Polansky, M., Kalmar, K., Giacino, J., Childs, N., Mercer, W., Novak, P., Maurer, P., Eifert, B., 2005. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. Arch Phys Med Rehabil 86, 453-462.

Whyte, J., Myers, R., 2009. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil 88, 410-418.

Wijdicks, E.F., 2002. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 58, 20-25.

Wijdicks, E.F., Bamlet, W.R., Maramattom, B.V., Manno, E.M., McClelland, R.L., 2005. Validation of a new coma scale: The FOUR score. Ann Neurol 58, 585-593.

Wijdicks, E.F., Hijdra, A., Young, G.B., Bassetti, C.L., Wiebe, S., 2006. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 67, 203-210.

Wijnen, V.J.M., Boxtel, G.J.M.v., Eilander, H.J., Gelder, B.d., 2007. Mismatch negativity predicts recovery from the vegetative state. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology 118, 597-605.

Wilhelm, B., Jordan, M., Birbaumer, N., 2006. Communication in locked-in syndrome: Effects of imagery on salivary pH. pp. 534-535.

Wolford, G., Morrison, F., 1980. Processing of unattended visual information. Mem Cognit 8, 521-527.

Wood, N., Cowan, N., 1995. The cocktail party phenomenon revisited: How frequent are attention shifts to one's own name in an irrelevant auditory channel. J Exp Psychol Learn Mem Cogn 21, 255-260.

Xu, J., Rasmussen, I.A., Lagopoulos, J., Haberg, A., 2007. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J Neurotrauma 24, 753-765.

Yamada, F., 1998. Frontal midline theta rhythm and eyeblinking activity during a VDT task and a video game: useful tools for psychophysiology in ergonomics. Ergonomics 41, 678-688.

Yamamoto, T., Katayama, Y., 2005. Deep brain stimulation therapy for the vegetative state. Neuropsychol Rehabil 15, 406-413.

Yingling, C.D., Hosobuchi, Y., Harrington, M., 1990. P300 as a predictor of recovery from coma. Lancet 336, 873.

Young, G., 2009. Coma. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness: Cognitive Neuroscience and Neuropathology. Elsevier, Oxford, pp. 137-150.

Zeman, A., 2001. Consciousness. Brain 124, 1263-1289.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Liao, W., Chen, Z., Shi, J., Liu, Y., 2009. Impaired perceptual networks in temporal lobe epilepsy revealed by resting fMRI. J Neurol 256, 1705-1713.

PUBLICATIONS SCIENTIFIQUES

Vegetative state

Audrey Vanhaudenhuyse, Mélanie Boly and Steven Laureys

Scholarpedia 2009, 4(1):4163.

Contents

Consciousness has two dimensions (Zeman, 2001): arousal or wakefulness (i.e., level of consciousness) and awareness (i.e., content of consciousness). Fig.1. In normal physiological states (green); level and content are positively correlated (with the exception of the oneiric activity during REM-sleep). Patients in pathological or pharmacological coma (i.e., general anesthesia) are unconscious because they cannot be awakened (red). The **vegetative state** (VS, blue) is a unique dissociated state of consciousness.

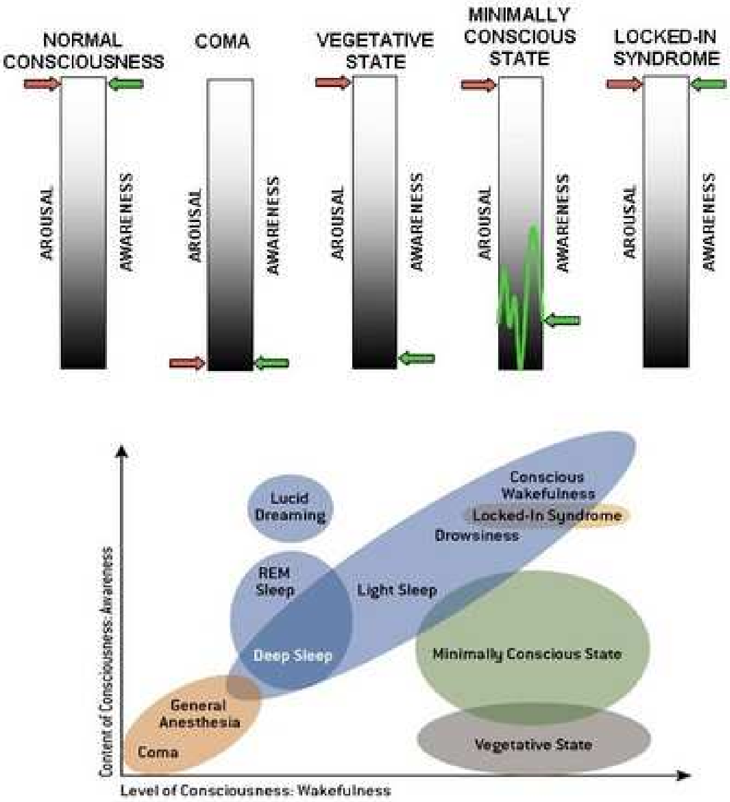


Figure 1: Illustration of the two major components of consciousness: the level of consciousness (i.e., arousal or wakefulness) and the content of consciousness (i.e., awareness).(Adapted from Laureys, 2005)

Progress in medicine has increased the number of patients who survive severe acute brain damage. Although the majority of these patients recover from coma within the first days after the insult, some permanently lose all brain functions (brain death), while others evolve to a state of 'wakeful unawareness' (vegetative state). Those who recover, typically progress through different stages before fully or partially (minimally conscious state) recovering consciousness. Exceptionally, patients may awaken from their coma fully aware but unable to move or speak – their only way to communicate is via small eye movements (locked-in syndrome) Fig.2.

An accurate and reliable evaluation of the level and content of consciousness in severely brain-damaged patients is of paramount importance for their appropriate management. The clinical evaluation of consciousness in non-communicative patients remains erroneous in 40% of case (Andrews et al., 1996; Childs and Mercer, 1996; Schnakers et al., 2007). Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination (i.e. assessing command following). The Glasgow Coma Scale (GCS - Teasdale et al., 1983) is the most used clinical evaluation scale in coma. The GCS has three components: eye, verbal and motor response to external stimuli. The best or highest responses are recorded. In chronic disorders of consciousness, other standardized clinical testing by means of validated scales such as the Coma Recovery Scale (CRS-R - Giacino et al. , 2004) or the Sensory Modality Assessment and Rehabilitation Technique (SMART - Gill-Thwaites and Munday, 2004) are recommended.

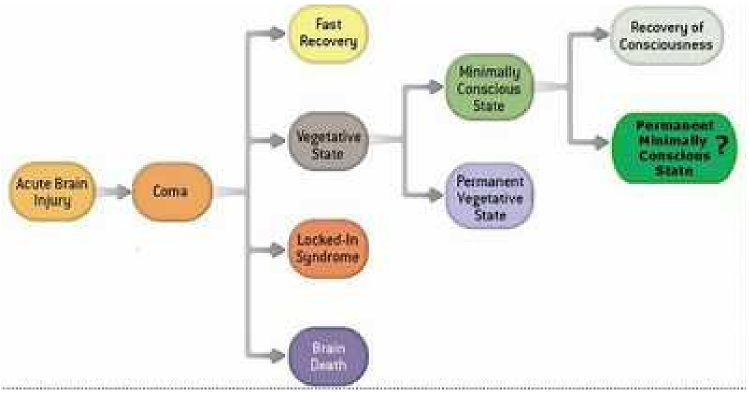


Figure 2: Chart of the different conditions that may follow acute brain injury. Coma does not last for more than a couple of days or weeks. For patients evolving to a vegetative state, the term "permanent vegetative state" has been used 3 months after non-traumatic insult or 1 year after traumatic brain injury. Vegetative patient who do recover classically evolve to a minimally conscious state. In rare cases, a person may develop locked-in syndrome, a nearly complete paralysis of the body's voluntary motor responses – only eye movements permit communication. (Taken from Laureys, 2007)

Brain death

Brain death means human death determined by neurological criteria. The diagnosis of brain death is based on the loss of all brainstem reflexes and the demonstration of continuing cessation of respiration – i.e. apnea testing - in a persistently comatose patient. There should be an evident cause of coma and confounding factors, such as hypothermia, drugs, electrolyte, and endocrine disturbances, should be excluded (Laureys, 2005). A repeat evaluation in six hours is advised, but this time period is considered arbitrary (The Quality Standards Subcommittee of the American Academy of Neurology, 1995). Electroencephalography (EEG), angiography, doppler sonography or scintigraphy are required as confirmatory neurophysiological tests when specific components of the clinical testing cannot be reliably evaluated. Confirmatory testing are recommended by a number of national societies to confirm the clinical diagnosis of brain death (Wijdicks, 2002). Brain death is classically caused by a massive brain lesion, such as trauma, intracranial hemorrhage or anoxia.

The EEG in brain death shows absent electrocortical activity with a sensitivity and specificity of around 90%. Functional neuroimaging typically show the absence of neuronal function in the whole brain in patients (i.e. the 'empty skull sign') (for a review, see Laureys et al., 2004) Fig.3.

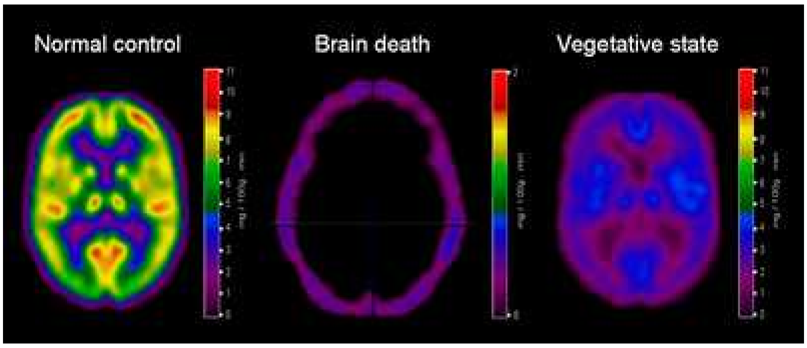


Figure 3: Differences in brain metabolism measured in brain death and the vegetative state, compared with healthy subjects. Patients in brain death show an 'empty-skull sign', clearly different from what is seen in vegetative patients, in whom brain metabolism is massively and globally decreased (to 40-50% of normal values) but not absent. (Taken from Laureys, 2005)

Defining death and organ donation are inextricably linked. Patients have to be declared dead before the removal of life-sustaining organs for transplantation. It is considered unethical to kill patients for their organs no matter how ill they are or how much good for others can be accomplished by doing so. To avoid conflict, transplant-surgeons are excluded from performing brain death examinations. Classically, organs are taken in patients who are declared brain death. In addition, the protocol for "donation after cardiac death" (or "donation after circulatory death," or "DCD." - University of Pittsburgh Medical Center policy and procedure manual, 1993) also permits to harvest organs in hopelessly comatose, but not brain dead, patients being maintained on positive-pressure ventilators in ICUs. They are allowed to die after their life-sustaining therapy (positive-pressure ventilation) is withdrawn in accordance with their wishes. Once their heart stops beating for a period of 2-10 minutes (that varies by protocol), they are declared dead and only then are their vital organs procured. As in brain dead organ donors, the organ procurement is performed only after the donor is declared dead. Here, confirmatory testing needs to document that the comatose patients has no chances of recovery (Bernat et al., 2006).

Diagnostic criteria for brain death (American Academy of Neurology guidelines, 1995)
Demonstration of coma
Evidence for the cause of coma
Absence of confounding factors (hypothermia, drugs, electrolyte, and endocrine disturbances)
Absence of brainstem reflexes
Absent motor responses
Apnea
A repeat evaluation in 6h
Confirmatory laboratory (when specific components of the clinical testing cannot be reliably evaluated)

Coma

Coma is a state of unarousable unresponsiveness in which the patient lies with the eye closed and has no awareness of self and surroundings (Posner et al., 2007). These patients will never open their eyes even when intensively stimulated. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least one hour. In general, comatose patients who survive begin to awaken and recover within 2 to 4 weeks. This recovery may sometimes go no further than the vegetative state or the minimally conscious state. There are two main causes for coma: (1) bihemispheric diffuse cortical or white matter damage or (2) brainstem lesions bilaterally affecting the subcortical reticular arousing systems.

Many factors such as etiology, the patient’s general medical condition, age, clinical signs and complimentary examinations influence the management and prognosis of coma. After 3 days of observation, absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, iso-electrical or burst suppression pattern EEG, bilateral absent cortical responses on somatosensory evoked potentials, and (for anoxic coma) biochemical markers such as high levels of serum neuron-specific enolase are known to herald bad outcome. Prognosis in traumatic coma survivors is known to be better than in anoxic cases (Laureys et al., 2008, Posner et al., 2007).

The EEG in patients who are in coma is characterized by an important general slowing. In addition, functional neuroimaging showed a global decrease of 50-70% in cerebral metabolism in coma patients, similar to values observed in general anesthesia Fig.4 (for a review, see Laureys et al., 2004).

Diagnostic criteria for coma (Posner et al., 2007)
Absence of eye opening even with intense stimulation
No evidence of awareness of self and their environment
Duration: at least one hour

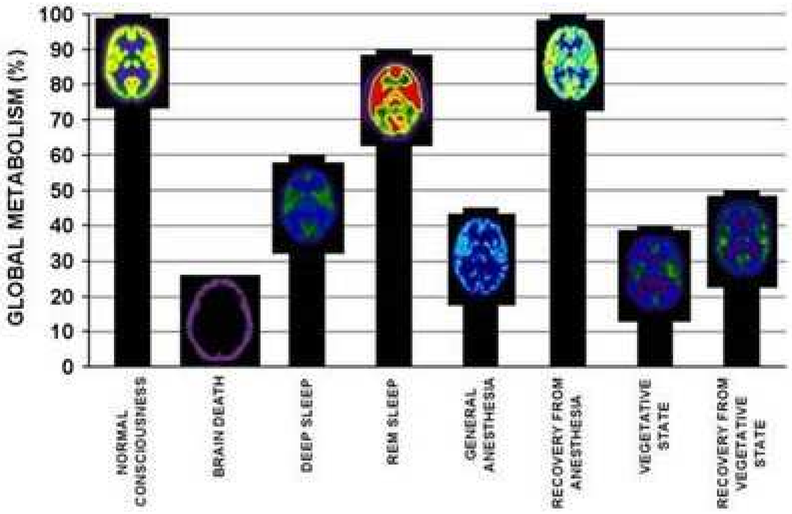


Figure 4: Brain function in conscious wakefulness; in brain death; physiological and pharmacological (general anesthesia) modulation of arousal reflecting massive global decreases in cortical metabolism (in REM sleep metabolic activity is paradoxically prominent); and in wakefulness without awareness (i.e., the vegetative state). The recovery from the vegetative state may occur without substantial increase in overall cortical metabolism, emphasizing that some areas in the brain are more important than others for the emergence of awareness. (Adapted from Laureys et al., 2004)

Vegetative state

After some days to weeks comatose patients will eventually open their eyes. When this return of “wakefulness without awareness of self and environment” is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state (The Multi-Society Task Force on PVS, 1994). The vegetative state may be a transition to further recovery, or not. It can be diagnosed soon after a brain injury and can be partially or totally reversible or it may progress to a permanent vegetative state or death. Many people in vegetative state regain consciousness in the first month after brain injury. However, after a month, the patient is said to be in a persistent vegetative state and the probability of recovery diminishes as more time passes. If patients show no sign of awareness one year after a traumatic brain injury or three months after brain damage from lack of oxygen, the chances of recovery are considered close to zero, and the patient is considered in a permanent vegetative state (The Multi-Society Task Force on PVS, 1994). However, rare cases of patients who recover after this interval have been reported (Childs and Mercer, 1996). It is very important to stress the difference between persistent and permanent vegetative state which are, unfortunately, too often abbreviated identically as PVS, causing unnecessary confusion (Laureys et al., 2000). It is now recommended to omit “persistent” and to describe a patient as having been vegetative for a certain time. When there is no recovery after a specified period (depending on etiology three to twelve months) the state can be declared permanent and withholding and withdrawal of treatment can be discussed (Jennett, 2005; Laureys et al., 2004).

We have at present no validated diagnostic nor prognostic markers for patients in a vegetative state. The chances of recovery depend on patient’s age, etiology (worse for anoxic causes), and time spent in the vegetative state. Recent data indicate that damage to the corpus callosum and brainstem indicate bad outcome in traumatic vegetative state (Carpentier et al., 2006; Kampfl et al., 1998).

Importantly, we have to stress that vegetative state is not brain death. Contrary to brain death, the vegetative state can be partially or completely reversible. Unlike vegetative patients who have their eyes spontaneously open, patients in brain death never show eye opening. Moreover, contrary to brain death, vegetative patients can breathe spontaneously without assistance and have preserved brainstem reflexes and hypothalamic functioning. Additionally, positron emission tomography (PET) studies have showed clear differences between brain metabolism of vegetative and brain death patients Fig.3. The so-called ‘empty-skull sign’ classically observed in brain death confirms the absence of neuronal function in the whole brain (Laureys et al., 2004). Such functional ‘decapitation’ is never observed in patients in a vegetative state.

Electroencephalography shows an important general slowing of the electrical brain activity of patients in vegetative state. Somatosensory evoked potentials may show preserved primary somatosensory cortical potentials and brainstem auditory evoked potentials often show preserved brainstem potentials in vegetative patients. Endogenous evoked potentials measuring for example the brain’s response to complex auditory stimuli such as the patient’s own name (as compared to other names) permits to record a so-called P300 response. Recent data show that the P300 is not a reliable marker of awareness but rather signs automatic processing, as it could be recorded in well-documented vegetative state patients who never recovered (Perrin et al., 2006).

Vegetative patients show substantially reduced (40–50% of normal values) but not absent overall cortical metabolism. In some vegetative patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes Fig.4. In addition, PET studies on pain perception have showed that healthy control subjects and patients in vegetative state didn’t demonstrate the same brain activity when they received a painful stimulation Fig.6. In patients in a vegetative state, the activity of primary somatosensory cortex was isolated and disconnected from the rest of the brain, in particular from the frontoparietal network believed to be critical for conscious perception (Laureys et al., 2002) Fig.5.

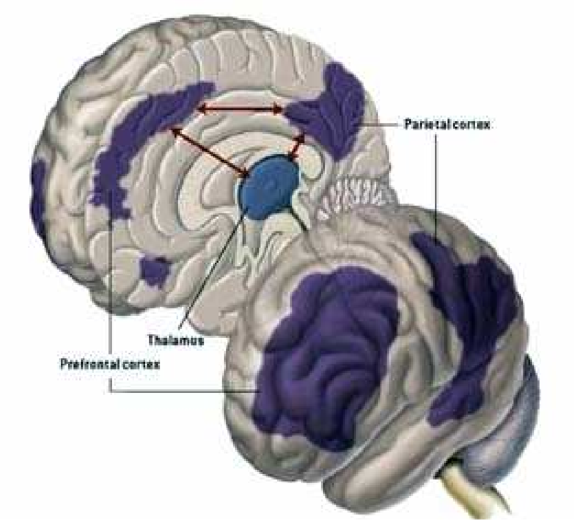


Figure 5: The common hallmark of the vegetative state is a metabolic dysfunctioning of a widespread cortical network encompassing medial and lateral prefrontal and parietal multi-modal associative areas. (Taken from Laureys, 2007)

Diagnostic criteria for the vegetative state (US Multi-Society Task Force on Persistent Vegetative State guidelines, 1994)
No evidence of awareness of self or environment and an inability to interact with others
No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
No evidence of language comprehension or expression
Presence of sleep-wake cycles
Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care
Bowel and bladder incontinence
Variably preserved cranial-nerve and spinal reflexes

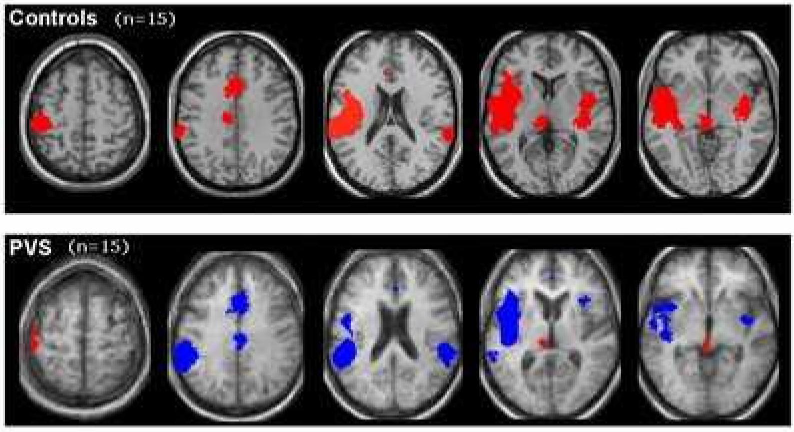


Figure 6: Healthy control subjects and patients in a vegetative state do not demonstrate the same brain activity when receiving a painful stimulation. In patients in a vegetative state, the activity of primary somatosensory cortex is isolated and disconnected from the rest of the brain. (Taken from Laureys et al., 2002)

Minimally conscious state

The criteria for the minimally conscious state were recently proposed in 2002 (Giacino et al.). The minimally conscious state describes patients who are unable to communicate their thoughts and feelings, but who demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment. Patients in a minimally conscious state have to show at least one of the following behaviors: oriented response to noxious stimuli, sustained visual pursuit, command following, intelligible verbalization or emotional or motor behaviors that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Like the vegetative state, the minimally conscious state may be chronic and sometimes permanent. At present, no time intervals for "permanent minimally conscious state" have been agreed upon. Some patients who have remained in the minimally conscious state for years were shown to slow recover to meaningful lives (Voss et al., 2006). The emergence from the minimally conscious state is defined by the ability to use functional interactive communication or functional use of objects (Giacino et al., 2002) Fig.7.

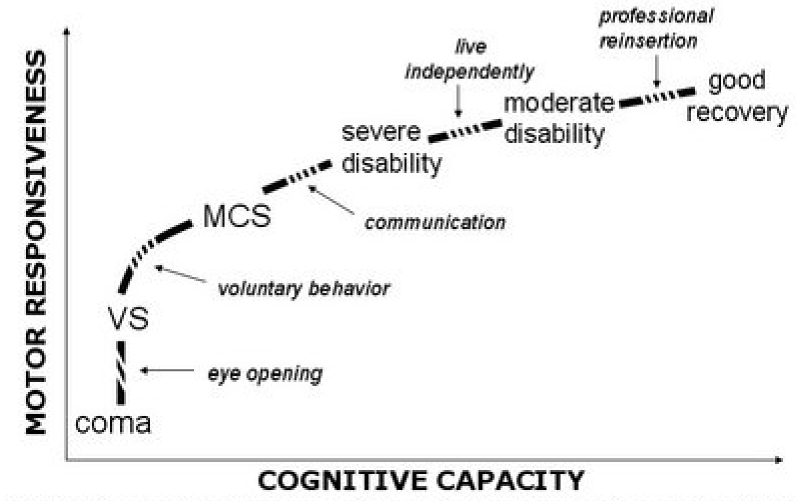


Figure 7: Different clinical entities encountered on the gradual recovery from coma, illustrated as a function of cognitive and motor capacities. Restoration of spontaneous or elicited eye-opening, in the absence of voluntary motor activity, marks the transition from coma to vegetative state (VS). The passage from the VS to the minimally conscious state (MCS) is marked by reproducible evidence of "voluntary behavior" on command following. Emergence from MCS is signaled by the return of functional communication or object use. (Taken from Laureys et al., 2005)

Given that the criteria for the minimally conscious state have only recently been introduced, there are few clinical studies of patients in this condition. Similar as for the vegetative state, traumatic etiology has a better prognosis than non-traumatic (anoxic) minimally conscious state. Preliminary data show that overall outcome is better than for the vegetative state (Giacino et al., 2002).

The electroencephalogram shows a general slowing of the electrical brain activity in patients in a minimally conscious state. Neuroimaging has shows that minimally conscious patients differ from vegetative patients in their metabolic activity in the precuneus and posterior cingulate cortex (Laureys et al., 2004). In addition, in patients in a minimally conscious state, auditory stimuli trigger higher-order cortical activity normally not observed in the vegetative state (Boly et al., 2005). In the same line, auditory stimuli with emotional valence (such as infant cries or the patient's own name (Laureys et al., 2004) or a narrative told by the patients mother (Schiff et al., 2005)) induce a much more widespread activation in patients in minimally conscious state than meaningless stimuli do Fig.8. This indicates that content does matter 'when talking to a patient in minimally conscious state'.

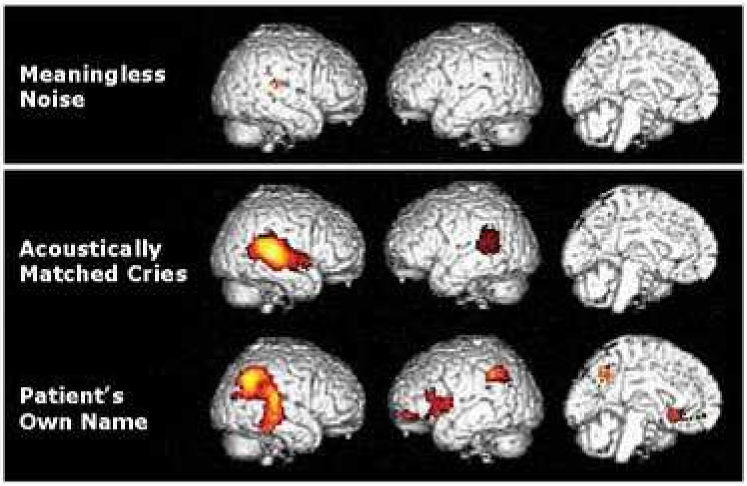


Figure 8: Brain activations during presentation of noise, infant cries, and the patient's own name. Stimuli with emotional valence (baby's cries and names) induce a much more widespread activation than does meaningless noise.(Taken from Laureys et al., 2004)

A recent fMRI study reported a youg women considered as being in a vegetative state while she showed indistinguishable brain activity from these observed in healthy people when we asked her to imaging playing tennis and visiting her house (Owen et al. , 2006) Fig.9. Despite the clinical diagnosis that the patient was in a vegetative state, she understood the tasks and repeatedly performed them and hence must have been conscious. A few months after the study, the patient evolved towards a minimally conscious state. The results of this study should not be misinterpreted as evidence that all patients in a vegetative state may actually be conscious. We have not observed any similar signs of awareness in functional scans of more than 60 other patients in a vegetative state studied at the University of Liège (Belgium). The most likely explanation of these results is that the patient was already beginning the transition to the minimally conscious state at the time of the experiment. A study conducted by Di et al. (2007) also indicated that the activation of higher-level brain regions during functional MRI seems to predict recovery to the minimally conscious state. In addition, MRI studies permit to visualize the extent of brain damage, and new advances in MRI scanning, such as diffusion tensor imaging and spectroscopy, can also offering prognostic information (Galanaud et al. , 2007). This technique can also shed light on mechanisms of recovery from the minimally conscious state. For example, an MRI diffusion tensor imaging study identified axonal regrowth in the brain of a patient who emerged from a minimally conscious state after 19 years of silence (Voss et al., 2006).

Diagnostic criteria for minimally conscious state (Aspen Neurobehavioral Conference Workgroup, 2002)
Clearly discernible evidence of awareness of self or environment, on a reproducible or sustained basis, by at least one of the following behaviors:
Purposeful behavior (including movements or affective behavior that occur in contingent relation to relevant environment stimuli and are not due to reflexive activity) such as: -Pursuit eye movement or sustained fixation occurring in direct response to moving or salient stimuli -Smiling or crying in response to verbal or visual emotional (but not neutral) stimuli -Reaching for objects demonstrating a relationship between object location and direction of reach -Touching or holding objects in a manner that accommodates the size and shape of the object -Vocalizations or gestures occurring in direct response to the linguistic content of questions
Command following
Gestural or verbal yes/no response (regardless of accuracy)
Intelligible verbalization
Emergence from MCS is signalled by the return of functional communication or object use

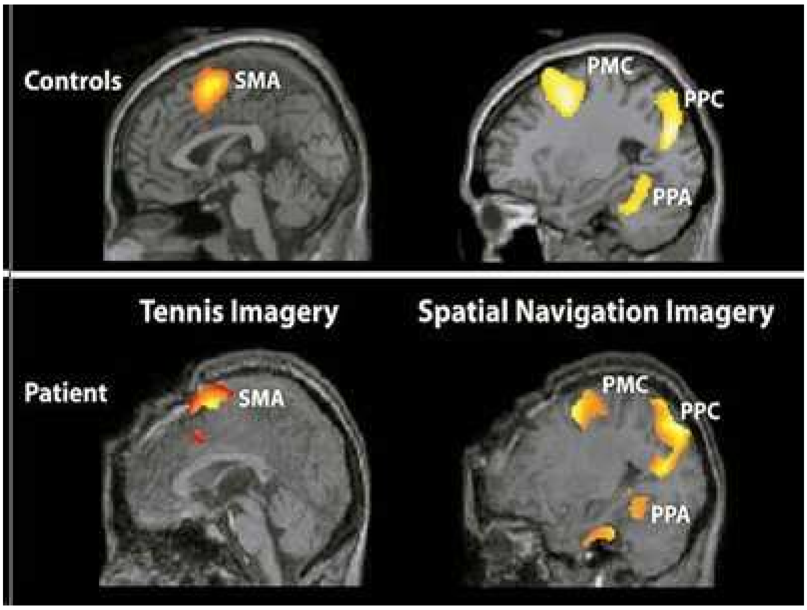


Figure 9: Owen et al. (2006) reported a women clinically considered in a vegetative state showed indistinguishable brain activity from these observed in healthy subject when asked to imaging playing tennis or visiting her house. A few months after the study, the patient recovered consciousness. (Taken from Owen et al., 2006)

Locked-in syndrome

The locked-in syndrome describes patients who are awake and conscious but have no means of producing speech, limb, or facial movements. Brainstem lesions are its most common cause. People with such lesions often remain comatose for some days or weeks, needing artificial respiration and then gradually wake up, albeit remaining paralyzed and voiceless, superficially resembling patients in a vegetative state. Locked-in patients can be divided into three categories (Bauer et al., 1979): (a) classical locked-in syndrome is characterized by quadriplegia and anarthria with eye coded communication; (b) incomplete locked-in syndrome permits remnants of voluntary responsiveness other than eye movement; and (c) total locked-in syndrome consists of complete immobility including all eye movements, combined with preserved consciousness. Once a locked-in syndrome patient becomes medically stable, and given appropriate medical care, life expectancy now is several decades. Even if the chances of good motor recovery are very limited, existing eye-controlled computer-based communication technology currently allows these patient to control their environment, use a word processor coupled to a speech synthesizer and access the world wide net. Neuropsychological testing batteries adapted and validated for eye-response communication, have shown preserved intellectual capacities in locked-in syndrome patients (Schnakers et al., 2008).

Recent surveys show that chronic locked-in syndrome patients self-report meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent (Bruno et al., 2008; Laureys et al., 2008).

According to some studies, the EEG does not consistently distinguishes the locked-in syndrome from the vegetative state (Gutling et al. , 1996). PET scanning has shown preserved metabolic cerebral functioning in a locked-in syndrome when compared to those in a vegetative state or minimally conscious state Fig.10.

Diagnostic criteria for locked-in syndrome (American Congress of Rehabilitation Medicine, 1995)
Presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor)
Aphonia or hypophonia
Quadriplegia or quadriparesis
Primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses
Preserved awareness of the environment

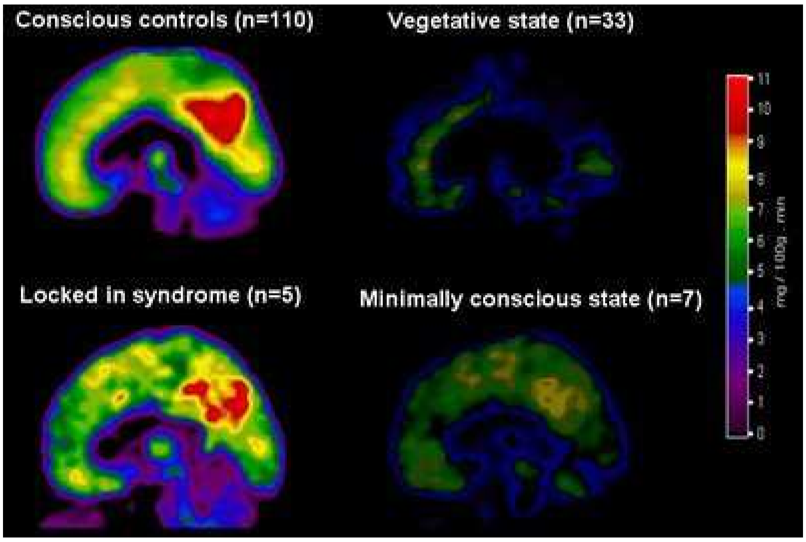


Figure 10: Resting cerebral metabolism in healthy individuals and patients in a vegetative state, locked-in syndrome, and minimally conscious state. In healthy conscious individuals and locked-in patients the medial posterior cortex (encompassing the precuneus and adjacent posterior cingulate cortex) is the most metabolically active region of the brain; in patients in vegetative state, this same area is the most dysfunctional. The precuneus and posterior cingulate cortex of patients in a minimally conscious state shows an intermediate metabolism, higher than in a vegetative state, but lower than in healthy subjects.(Taken from Laureys et al., 2004)

Treatment

Some studies have reported cases of patients with chronic disorders of consciousness who exhibited unexpected behavioral amelioration after administration of amantadine (Whyte et al., 2005; Zafonte et al., 1998). Amantadine, a mainly dopaminergic agent, was shown to increase metabolic activity in chronic minimally conscious patients (Schnakers et al., 2008). Placebo controlled randomized trials are needed before making assertive conclusions about the effectiveness of the drug in disorders of consciousness patients. Similarly, some studies reported that administration of zolpidem, a non-benzodiazepine sedative drug, may improve arousal and cognition of brain-injured patients (Clauss and Nel, 2006).

An other non-pharmacological treatment consist on the deep brain stimulation of the thalamus. A recent case report by Nicholas Schiff and colleagues from New York showed its efficacy in a chronic post-traumatic minimally conscious patient (Schiff et al., 2007). However, at present, this remains research and awaits further confirmation. It has not been shown effective in the vegetative state.

Future challenges

Brain death, comatose, vegetative and minimally conscious states represent different pathological alterations of both dimensions of consciousness (involving arousal and awareness) or, for locked-in states, of the motor signs of consciousness. The clinical evaluation of conscious perception and cognition in these patients is difficult and erroneous in 40% of case. Electrophysiological and functional neuroimaging studies are increasing our understanding of the neural correlates of arousal and awareness and will improve the diagnosis, prognosis and management these challenging patients. At present, much more data and methodological validation is awaited before functional neuroimaging studies can be proposed to the medical community as a tool to disentangle conscious from unconscious patients. In the same line, we need much more data before we make any assertive conclusions about the effect of pharmacological and non-pharmacological treatment in patients in altered state of consciousness.

References

Andrews K, Murphy L, Munday R and Littlewood C: Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. Bmj. 313: 13-6, 1996.

Bauer G, Gerstenbrand F and Rumpl E: Varieties of the locked-in syndrome. J Neurol. 221: 77-91, 1979.

Bernat JL, D'Alessandro AM, Port FK, Bleck TP, Heard SO, Medina J, Rosenbaum SH, Devita MA, Gaston RS, Merion RM et al.: Report of a National Conference on Donation after cardiac death. Am J Transplant. 6: 281-91, 2006.

Bruno M, Bernheim JL, Schnakers C and Laureys S: Locked-in: don't judge a book by its cover. J Neurol Neurosurg Psychiatry. 79: 2, 2008.

Carpentier A, Galanaud D, Puybasset L, Muller JC, Lescot T, Boch AL, Riedl V, Cornu P, Coriat P, Dormont D et al.: Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". J Neurotrauma. 23: 674-85, 2006.

Childs NL and Mercer WN: Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs [letter; comment]. BMJ. 313: 944, 1996.

Childs NL and Mercer WN: Brief report: late improvement in consciousness after post-traumatic vegetative state. N Engl J Med. 334 (1): 24-25, 1996.

Clauss R and Nel W: Drug induced arousal from the permanent vegetative state. NeuroRehabilitation. 21: 23-8, 2006.

Di HB, Yu SM, Weng XC, Laureys S, Yu D, Li JQ, Qin PM, Zhu YH, Zhang SZ and Chen YZ: Cerebral response to patient's own name in the vegetative and minimally conscious states. Neurology. 68: 895-9, 2007.

Galanaud D, Naccache L and Puybasset L: Exploring impaired consciousness: the MRI approach. Curr Opin Neurol. 20: 627-31, 2007.

Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD et al.: The minimally conscious state: definition and diagnostic criteria. Neurology. 58: 349-53, 2002.

Giacino JT, Kalmar K and Whyte J: The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 85: 2020-9, 2004.

Gill-Thwaites H and Munday R: The Sensory Modality Assessment and Rehabilitation Technique (SMART): a valid and reliable assessment for vegetative state and minimally conscious state patients. Brain Inj. 18: 1255-69, 2004.

Gutling E, Isenmann S and Wichmann W: Electrophysiology in the locked-in-syndrome. Neurology. 46: 1092-101, 1996.

Jennett B: The assessment and rehabilitation of vegetative and minimally conscious patients: Definitions, diagnosis, prevalence and ethics. Neuropsychological Rehabilitation. 15: 163-165, 2005.

Kampfl A, Schmutzhard E, Franz G, Pfausler B, Haring HP, Ulmer H, Felber S, Golaszewski S and Aichner F: Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. Lancet. 351: 1763-7, 1998.

Laureys S: The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cognitive Science. 9: 556-9, 2005.

Laureys S: Science and society: death, unconsciousness and the brain. Nat Rev Neurosci. 6: 899-909, 2005.

Laureys S: Eyes open, brain shut. Sci Am. 296: 84-9, 2007.

Laureys S, Boly M, Moonen G and Maquet P: Arousal and awareness in coma and post-comatose states, in Squire EEL: New Encyclopedia of Neuroscience 2008.

Laureys S, Faymonville ME and Berre J: Permanent vegetative state and persistent vegetative state are not interchangeable terms. British Medical Journal, 2000.

Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, Degueldre C, Aerts J, Luxen A, Franck G et al.: Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage. 17: 732-41, 2002.

Laureys S, Owen AM and Schiff ND: Brain function in coma, vegetative state, and related disorders. Lancet Neurol. 3: 537-46, 2004.

Laureys S, Perrin F, Faymonville ME, Schnakers C, Boly M, Bartsch V, Majerus S, Moonen G and Maquet P: Cerebral processing in the minimally conscious state. Neurology. 63: 916-8, 2004.

Laureys S, Perrin F, Schnakers C, Boly M and Majerus S: Residual cognitive function in comatose, vegetative and minimally conscious states. Curr Opin Neurol. 18: 726-733, 2005.µ

Owen AM, Coleman MR, Boly M, Davis MH, Laureys S and Pickard JD: Detecting awareness in the vegetative state. Science. 313: 1402, 2006.

Perrin F, Schnakers C, Schabus M, Degueldre C, Goldman S, Bredart S, Faymonville ME, Lamy M, Moonen G, Luxen A et al.: Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol. 63: 562-9, 2006.

Posner JB, Saper CB, Schiff N and Plum F: The diagnosis of stupor and coma, 4th ed., 2007.

Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J et al.: Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 448: 600-3, 2007.

Schiff ND, Rodriguez-Moreno D, Kamal A, Kim KH, Giacino JT, Plum F and Hirsch J: fMRI reveals large-scale network activation in minimally conscious patients. Neurology. 64: 514-23, 2005.

Schnakers C, Hustinx R, Vandewalle G, Majerus S, Moonen G, Boly M, Vanhaudenhuyse A and Laureys S: Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 79: 225-7, 2008.

Schnakers C, Majerus S, Goldman S, Boly M, Van Eeckhout P, Gay S, Pellas F, Bartsch V, Peigneux P, Moonen G et al.: Cognitive function in the locked-in syndrome. J Neurol. 255: 323-30, 2008.

Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G and Laureys S: Misdiagnosis of the vegetative and minimally conscious state in Belgium. Neurology. submitted, 2007.

Teasdale G, Jennett B, Murray L and Murray G: Glasgow coma scale: to sum or not to sum. Lancet. 2: 678., 1983.

The Multi-Society Task Force on PVS: Medical aspects of the persistent vegetative state (1). N. Engl. J. Med. 330: 1499-508, 1994.

The Quality Standards Subcommittee of the American Academy of Neurology: Practice parameters for determining brain death in adults (summary statement). Neurology. 45: 1012-1014, 1995.

University of Pittsburgh Medical Center policy and procedure manual: Management of terminally ill patients who may become organ donors after death. Kennedy Inst Ethics J. 3: A1-15, 1993.

Voss HU, Uluc AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, Heier LA, Beattie BJ, Hamacher KA, Vallabhajosula S et al.: Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest. 116: 2005-11, 2006.

Whyte J, Katz D, Long D, DiPasquale MC, Polansky M, Kalmar K, Giacino J, Childs N, Mercer W, Novak P et al.: Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. Arch Phys Med Rehabil. 86: 453-62, 2005.

Wijdicks EF: Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology. 58: 20-5, 2002.

Zafonte RD, Watanabe T and Mann NR: Amantadine: a potential treatment for the minimally conscious state. Brain Inj. 12: 617-21, 1998.

Zeman A, Consciousness. Brain. 124: 1263-89., 2001

Recommended Reading

Laureys, S.; Owen, A.M.; and Schiff, N.D. (2004a) Brain function in coma, vegetative state, and related disorders. Lancet Neurol, 3(9):537-46

Laureys, S. (2005) The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cognitive Science, 9(12):556-9 Fins, J.J. Constructing an ethical stereotaxy for severe brain injury: balancing risks, benefits and access. Nat Rev Neurosci, 4(4):323-7, 2003.

Laureys, S. Science and society: death, unconsciousness and the brain. Nat Rev Neurosci, 6(11):899-909, 2005.

Owen, A.M.; Coleman, M.R.; Boly, M.; Davis, M.H.; Laureys, S.; and Pickard, J.D. Detecting awareness in the vegetative state. Science, 313(5792):1402, 2006.

Bernat, JL. Chronic disorders of consciousness. Lancet, 367 (9517): 1181-92, 2006.

Laureys, S. Eyes open, brain shut. Sci Am, 296(5):84-9, 2007.

Posner JB, Saper CB, Schiff N and Plum F: The diagnosis of stupor and coma, 4th ed., 2007.

Owen, AM. Disorders of consciousness. Ann N Y Acad Sci. 1124: 225-38, 2008.

Réanimation (2007) **16**, 527—532

ELSEVIER MASSON

Disponible en ligne sur www.sciencedirect.com

ScienceDirect

journal homepage: http://france.elsevier.com/direct/REAURG/

MISE AU POINT

Détecter les signes de conscience chez le patient en état de conscience minimale

Detecting consciousness in minimally conscious patients

A. Vanhaudenhuyse[a], **C. Schnakers**[a], **M. Boly**[a], **F. Perrin**[b], **S. Brédart**[c], **S. Laureys**[a,*]

[a] *Coma science group, centre de recherches du cyclotron, université de Liège, Sart Tilman B30, 4000 Liège, Belgique*
[b] *UMR5020 « Neurosciences sensorielles, comportement, cognition », université Claude-Bernard, 69366 Lyon, France*
[c] *Département des sciences cognitives, université de Liège, 4000 Liège, Belgique*

Disponible sur Internet le 1 Octobre 2007

MOTS CLÉS
État de conscience minimale ;
État végétatif ;
Conscience de soi ;
Évaluations comportementales ;
Électroencéphalogramme ;
IRM fonctionnelle ;
PET

Résumé Aujourd'hui, environ un tiers des patients en état de conscience minimale sont encore mal diagnostiqués et considérés comme végétatifs. Il ressort de la littérature que les stimuli autoréférentiels, comme le suivi de son reflet dans un miroir, sont un bon moyen pour détecter les premiers signes de conscience chez ces patients non communicatifs. Les études comportementales, électroencéphalographiques et en neuro-imagerie démontrent qu'il est possible de déterminer si les patients sont conscients ou non à l'aide de stimuli tels que le propre prénom et le propre visage. Nous proposons que dans l'évaluation clinique de routine, la poursuite visuelle du patient soit testée à l'aide d'un miroir.

© 2007 Société de réanimation de langue française. Publié par Elsevier Masson SAS. Tous droits réservés.

KEYWORDS
Minimally conscious state;
Vegetative state;
Self-consciousness;
Behavioral assessment;
Electroencephalogram;
Functional MRI;
PET

Summary At present, about a third of minimally conscious patients are erroneously diagnosed as being in a vegetative state. The use of autoreferential stimuli such as following one's reflection in a mirror permits to detect early signs of consciousness in these noncommunicative patients. Behavioral, electroencephalographic and neuroimaging studies using patients' own name and own face showed that it is possible to differentiate between conscious and unconscious brain-damaged patients.

© 2007 Société de réanimation de langue française. Publié par Elsevier Masson SAS. Tous droits réservés.

---

[*] Auteur correspondant.
Adresse e-mail : steven.laureys@ulg.ac.be (S. Laureys).

1624-0693/$ — see front matter © 2007 Société de réanimation de langue française. Publié par Elsevier Masson SAS. Tous droits réservés.
doi:10.1016/j.reaurg.2007.09.010

Introduction

Des examens paracliniques multimodaux peuvent aider le clinicien à détecter les signes de conscience et donc lui permettre d'améliorer son diagnostic. En effet, la difficulté à déceler la présence de conscience se traduit par de fréquentes erreurs diagnostiques d'état végétatif (EV) [1,2] et de *locked-in syndrome* [3]. L'évaluation des fonctions cérébrales résiduelles chez les patients en état de conscience altérée n'étant pas aisée, les études électrophysiologiques et les études en neuro-imagerie fonctionnelle offrent la possibilité d'évaluer objectivement les fonctions cérébrales préservées chez les patients en état de conscience altérée (pour des revues récentes, voir [4—7]). Dans cet article, nous proposons, tout d'abord, de définir brièvement la conscience de soi et de l'environnement telles qu'elles peuvent être évaluées au chevet du patient. Ensuite, nous définirons les entités rencontrées après une lésion cérébrale. Enfin, nous discuterons de l'importance des stimuli autoréférentiels pour l'évaluation de la conscience de soi en présentant les éléments objectivés lors des évaluations comportementales, électrophysiologiques ainsi qu'en neuro-imagerie.

États de conscience altérée

À la suite d'une lésion cérébrale sévère, le patient évoluera du coma à la récupération en passant par plusieurs stades (Fig. 1). Le coma est caractérisé par une absence complète d'éveil ainsi qu'une absence de conscience de soi et de l'environnement [8]. Le coma peut se prolonger de quelques jours à quelques semaines. Si le réveil du patient ne s'accompagne pas d'une récupération de la conscience, nous parlons alors d'état végétatif. L'état végétatif se différencie du coma par la présence du cycle veille—sommeil. Le patient végétatif ne démontre aucun signe de conscience ni de lui-même ni de son environnement [9]. Cet état peut être chronique ou une transition vers une récupération future.

Certains patients sévèrement cérébrolésés ne correspondent pas aux critères diagnostiques de l'EV. En effet, ces patients démontrent des signes clairs de conscience de leur environnement et d'eux-mêmes. C'est en 2002 qu'ont été définis les critères de l'état de conscience minimale (ECM). L'ECM se distingue de l'EV par la présence de comportements incohérents mais reproductibles et soutenus durant une période assez longue pour ne pas les confondre avec des mouvements réflexes [10]. Un patient en ECM est capable de localiser des stimulations nociceptives, suivre du regard un objet déplacé dans son champ visuel, démontrer des comportements émotionnels adaptés et répondre à des commandes simples (par exemple : serrer la main, ouvrir la bouche, etc.). La sortie de l'ECM est caractérisée par la présence fiable et consistante d'une communication fonctionnelle ou de l'utilisation fonctionnelle de deux objets de la vie courante. De plus, si l'activité métabolique globale cérébrale ne permet pas de différentier l'EV de l'ECM, les activations régionales du précunéus et du cortex cingulaire antérieur semblent être la clé pour différencier un patient conscient d'un patient inconscient [11].

Certains patients, plus rares, entrent en *locked-in syndrome*. Ce syndrome est caractérisé par une quadriplégie, une diplégie faciale et une anarthrie. Ces patients sont éveillés et présentent une conservation de la conscience et des facultés intellectuelles, mais ne peuvent communiquer que par le clignement des paupières ou des mouvements palpébraux [12].

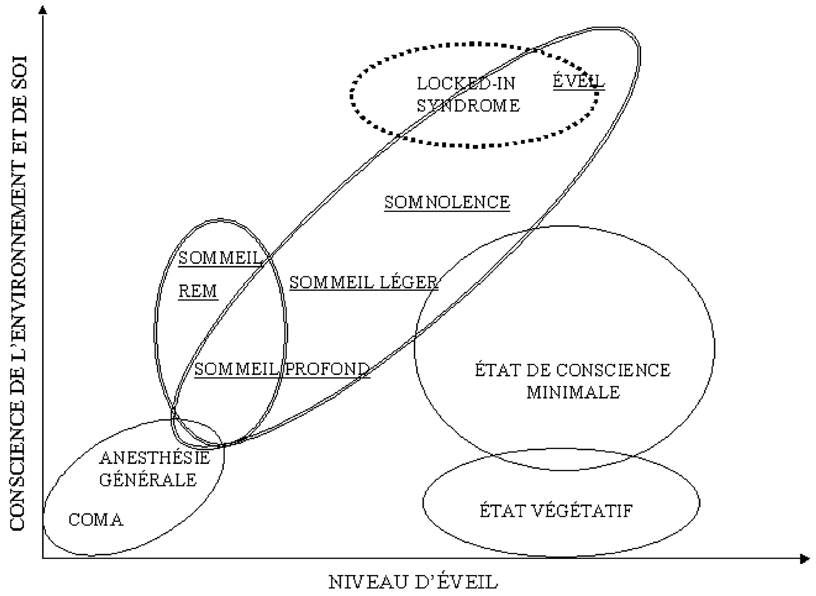


Figure 1 Corrélation du niveau d'éveil avec la conscience de soi et de l'environnement.
Ce graphique illustre les deux composantes majeures de la conscience : le niveau d'éveil et la conscience de soi et de l'environnement. À l'exception du sommeil REM, le niveau d'éveil et la conscience sont positivement corrélés dans les états physiologiques normaux (soulignés dans le graphique) et chez les patients *locked-in*. Les patients en coma et sous anesthésie générale sont inconscients car leur niveau d'éveil est nul. L'état végétatif ainsi que l'état de conscience minimale illustrent une dissociation plus ou moins importante de l'éveil et de la conscience.

Conscience et conscience de soi

Selon Zeman, la conscience a deux composantes [13] : l'éveil ou vigilance (*arousal* — niveau de conscience) et la conscience de soi et de l'environnement (*awareness* — contenu de la conscience) (Fig. 1). La conscience de soi implique une reconnaissance de soi mais fait également appel à des processus plus complexes, tels que le fait d'être conscient de sa conscience et de celle des autres. Plus précisément, Zeman différencie cinq éléments dans la conscience de soi [14] :

- la conscience qu'il existe d'autres consciences que la nôtre ;
- notre capacité de répondre adéquatement à des stimuli de l'environnement ;
- notre aptitude à reconnaître notre corps comme étant le nôtre ;
- la métaconscience nous permet de comprendre nos comportements et ceux des autres en terme de désirs et croyances ;
- la connaissance que nous avons de nous-mêmes comme le narrateur de notre propre vie.

Dans le cadre de cette revue de la littérature sur la conscience de soi chez des patients en ECM, nous nous centrerons sur la troisième définition de Zeman, à savoir la conscience de soi comme reconnaissance de soi (par exemple, la reconnaissance de notre reflet dans un miroir ou la réaction à notre prénom).

Un des premiers signes de récupération de la conscience est l'apparition de comportements spécifiques en réponse à des stimuli autoréférentiels [15]. À ce jour, deux catégories de stimuli ont été utilisées pour l'étude de la conscience de soi : le propre prénom et le propre visage. Lors des interactions sociales quotidiennes, entendre notre propre prénom attire notre attention et stimule la conscience de soi. En effet, ce prénom est chargé d'une signification personnelle ainsi que d'un contenu émotionnel pour chacun d'entre-nous. Par exemple, la plupart des gens remarquent lorsque l'on prononce leur prénom lors d'une conversation à laquelle ils n'avaient pas pris part et dont ils ne faisaient pas consciemment attention (phénomène *cocktail party*). Quoique le propre prénom ne soit pas, au sens propre, un stimulus qui capture notre attention de façon automatique, il provoque une réaction de surprise lorsqu'il apparaît dans un contexte où il n'est pas attendu, en tout cas lors de ses premières occurrences. Par ailleurs, des études récentes suggèrent que les visages sont également propices à capter l'attention [16] et que le propre visage est particulièrement efficace à cet égard [17].

Évaluation comportementale

L'utilisation d'échelles comportementales permet aux cliniciens de statuer sur la conscience des patients non communicatifs (pour une revue, voir [18]). Le problème de ces échelles est qu'elles utilisent des stimuli différents pour tester des aptitudes identiques chez les patients. Cette absence de consensus contribue au taux important d'erreurs diagnostiques mis en évidence par plusieurs études [1,2]. La poursuite visuelle fait partie de ces comportements testés par autant de techniques qu'il n'y a d'échelles. Pourtant, un des premiers signes de conscience apparaissant chez les patients en ECM est justement la poursuite visuelle. Considérons la *Glasgow coma scale* (GCS) [19], celle-ci n'évalue pas la poursuite visuelle. Alors que la *Full Outline of Unresponsiveness* (FOUR) [20], échelle récente et pratique pour l'évaluation clinique de routine, teste la poursuite visuelle du patient en lui demandant de suivre un doigt du regard. D'autres échelles, plus sensibles mais dont la passation est plus longue, comme la *Coma Recovery Scale-Revised* (CRS-R) [21] et la *Wessex Head Injury Matrix* (WHIM) [22] emploient un miroir ou une personne se déplaçant dans la pièce ou encore un objet. Nous avons démontré que l'utilisation d'un stimulus autoréférentiel comme dans la CRS-R (son propre reflet dans un miroir) était significativement plus puissante qu'un stimulus neutre (un objet) pour détecter cet indice de conscience[1] (Fig. 2). Dans cette étude, de tous les patients ECM présentant une poursuite visuelle, 93 % poursuivaient un miroir alors que seulement 65 % traquaient un objet neutre. Dès lors, environ un quart des patients ne poursuivant uniquement que leur reflet auraient été diagnostiqués en état végétatif puisqu'ils ne démontraient aucun autre signe de conscience. Cette étude souligne l'importance de l'utilisation de stimuli autoréférentiels pour détecter les signes de conscience chez des patients non communicatifs. Nous suggérons donc aux cliniciens d'utiliser un miroir lors de l'évaluation des patients postcomateux.

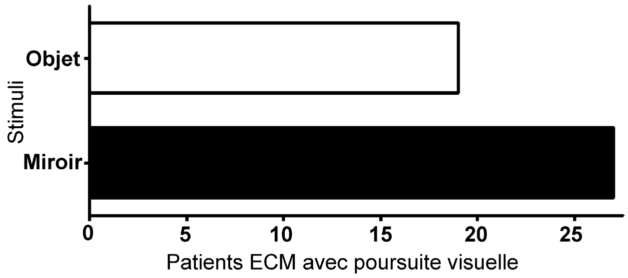


Figure 2 Stimuli autoréférentiels et poursuite visuelle. La poursuite visuelle est significativement mieux détectée chez les patients en état de conscience minimale lorsque l'on utilise un miroir. Vingt-sept patients traquent un miroir alors que seulement 19 traquent un objet neutre.

Potentiels évoqués

Les potentiels évoqués (PE) offrent la possibilité d'étudier de manière objective les mécanismes cérébraux sous-tendant le traitement de stimuli extérieurs, notamment chez les patients non communicatifs. Les PE traduisent la dynamique temporelle des processus électricocérébraux évoqués par des stimuli sensoriels, sans qu'une réponse comportementale explicite ne soit nécessaire. L'onde P300 est particulièrement intéressante car elle apparaît lorsque les sujets détectent un stimulus rare dans une série de

---

[1] Vanhaudenhuyse A, Schnakers C, Brédart S, Laureys S. Visual tracking in the minimally conscious state: use of a mirror. J Neurol Neurosurg Psychiatry (soumise pour publication).

stimuli réguliers [23]. L'amplitude de cette onde est particulièrement grande lorsque le stimulus déviant est le prénom du sujet [24].

Récemment, l'aptitude à détecter son propre prénom a été étudiée chez des patients non communicatifs. Dans notre paradigme, nous présentions le propre prénom ainsi que d'autres prénoms à des patients en état de conscience altérée [25]. Ainsi, nous avons enregistré une P300 en réponse au propre prénom chez tous les patients *locked-in*, en état de conscience minimale et même chez certains patients en état végétatif. Précisons que la latence de la P300 observée dans l'EV et l'ECM était retardée par rapport à la P300 des sujets sains. Cette étude, confirmée par d'autres travaux [26,27], souligne le fait que les processus d'identification de stimuli autoréférentiels sont partiellement préservés chez des patients souffrant de lésions cérébrales. De plus, Holeckova et al. ont mis en évidence que l'amplitude de la P300 chez des sujets sains augmentait lorsque le prénom du sujet était prononcé par une voix familière [28]. Lors des enregistrements de PE, nous devrions donc favoriser le propre prénom dit par un proche du patient plutôt que par le clinicien afin d'augmenter les chances d'apparition de la P300.

Cependant, nous devons rester prudents quant à l'interprétation de la P300 comme indice de processus conscient chez les patients cérébrolésés. En effet, Brazdil et al. ont démontré que l'onde P300 pouvait apparaître dans des processus inconscients comme la perception subliminale [29]. Dès lors, la seule conclusion que nous pouvons tirer est que la présence d'une P300 chez les patients EV et ECM reflète au moins un processus cérébral automatique de la compréhension langagière.

Neuro-imagerie fonctionnelle

Actuellement, les stimuli autoréférentiels ne sont encore que très peu utilisés en neuro-imagerie fonctionnelle chez des patients en état de conscience altérée. Néanmoins, les études déjà réalisées sont prometteuses. En effet, les études en neuro-imagerie semblent offrir une nouvelle mesure objective des processus cérébraux complexes ainsi qu'un outil pour différencier les patients conscients — ECM, des patients inconscients — EV.

Nous avons utilisé la tomographie par émission de positons (TEP) chez un patient en ECM, six mois après une hémorragie frontale gauche. Nous avons montré qu'un stimulus autoréférentiel auditif, tel que le prénom du patient, provoquait une activation plus étendue que des stimuli émotionnels, tels que le cri d'un bébé, et des stimuli sans signification [15]. Chez ce patient, l'écoute de son prénom activait le précuneus, les cortex cingulaire antérieur, mésiofrontal, temporopariétal droit et préfrontal dorsolatéral gauche ainsi que les gyri angulaires bilatéraux (Fig. 3). Plusieurs études en neuro-imagerie ont démontré l'implication du précuneus et du cortex cingulaire antérieur adjacent dans les processus autoréférentiels [30,31]. De plus, cette région cérébrale est l'une des plus actives dans l'éveil conscient [32] et une des moins actives dans les états

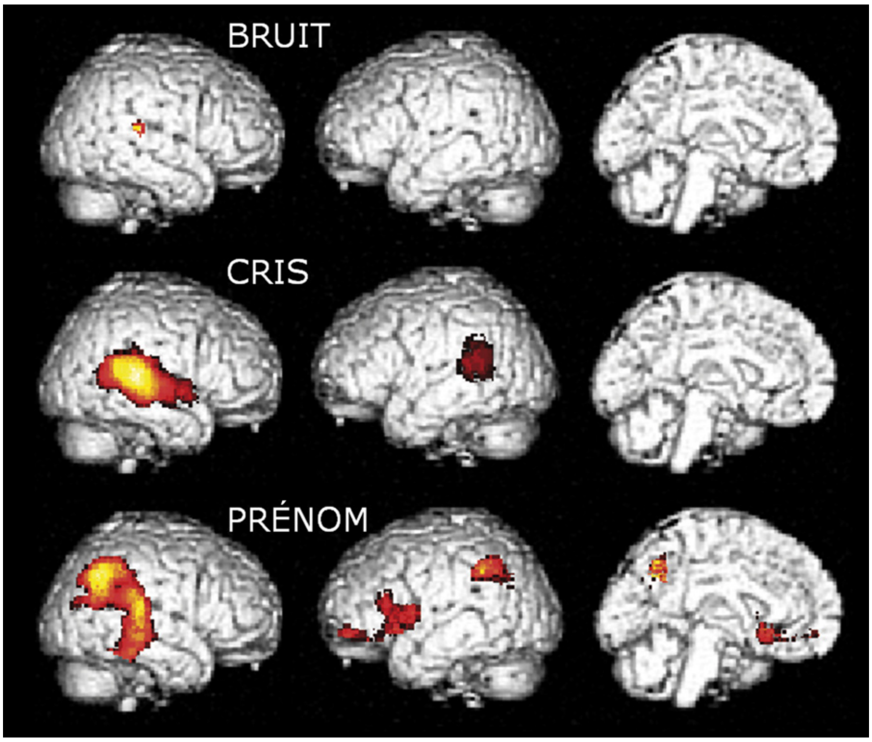


Figure 3 Augmentation de l'activité cérébrale lors de l'écoute de son propre prénom chez un patient en état de conscience minimale.
Chez un patient en état de conscience minimale, l'écoute de son propre prénom active significativement plus le précuneus, les cortex cingulaire antérieur, mésiofrontal, temporopariétal droit et préfrontal dorsolatéral gauche ainsi que les gyri angulaires bilatéraux que dans les conditions où il entend un stimulus neutre et un cri de bébé [15].

de conscience altérée comme le sommeil à mouvements oculaires rapides (*rapid eye movement sleep*, REM) ou le sommeil profond [33], en EV [34], en hypnose [35] et en anesthésie générale [36]. Par ailleurs, Schiff et al. ont observé que ces activations étaient plus importantes en présence de stimuli émotionnels comme l'écoute de récits lus par une voix familière et contenant des informations personnelles [37]. Plus récemment, Di et al. ont mis en évidence une activation des aires associatives, en plus du cortex auditif primaire, chez quatre patients ECM lorsqu'ils entendaient leur propre prénom mais également chez cinq patients végétatifs qui, quelques mois plus tard, ont récupéré [38]. De plus, Owen et al. ont démontré qu'en utilisant des paradigmes actifs comme demander à une patiente d'imaginer jouer au tennis ou d'imaginer visiter sa maison, il était possible de détecter des signes cérébraux de conscience alors qu'aucun indice n'avait été décelé lors des évaluations cliniques chez cette patiente en EV [39]. Tout comme les patients en EV étudiés par Di et al., la patiente d'Owen et al. est entrée en ECM peu de temps après l'étude. L'IRM fonctionnelle semble donc être un outil intéressant pour prédire la récupération de conscience chez les patients en EV.

Conclusion

L'évaluation de la conscience et de la conscience de soi chez les patients sévèrement cérébrolésés est capitale pour une bonne prise en charge et un traitement approprié. La pratique clinique nous montre que la reconnaissance des signes de conscience de soi et de l'environnement chez les patients en état de conscience altérée peut être très difficile. En effet, seule la personne elle-même sait qu'elle est consciente. Cette difficulté à détecter la présence de signes de conscience est la source d'encore beaucoup d'erreurs diagnostiques. Le niveau d'éveil de ces patients est souvent fluctuant et leurs réponses motrices restent limitées ou incohérentes.

Dans un premier temps, il nous semble important d'uniformiser les stimuli employés lors des évaluations comportementales au chevet du patient. Déterminer et utiliser les stimuli les plus sensibles aux indices comportementaux de conscience aiderait les cliniciens à préciser leur diagnostic et permettrait d'optimiser la prise en charge des patients non communicatifs. L'utilisation du miroir pour évaluer la capacité du patient à poursuivre visuellement devrait être systématique.

De plus, la conscience n'est pas un phénomène de « tout ou rien », son évaluation ne se base que sur l'interprétation des comportements observés. Dès lors, l'utilisation de l'électroencéphalographie et de la neuro-imagerie pourrait être d'un grand secours pour définir si un patient est conscient ou non. Toutefois, la limite des études actuelles est l'utilisation de paradigmes passifs difficilement interprétables puisque les résultats obtenus ne reflètent pas nécessairement des mécanismes volontaires. Il serait judicieux, dans les études à venir, d'utiliser des paradigmes où l'on demanderait aux patients de faire quelque chose activement comme Owen et al. l'ont fait pour une patiente végétative [39]. Enfin, soulignons l'intérêt de l'IRMf pour prédire la récupération de conscience des patients en EV.

Remerciements

Cette recherche est soutenue par le Fonds national de la recherche scientifique de Belgique (FNRS) et l'Action de recherche concertée belge de la communauté française (ARC 06/11-340). SL est maître de recherches auprès du FNRS, SB est professeur à l'université de Liège et MB aspirante FNRS.

Références

[1] Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993;43:1465—7.
[2] Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 1996;313:13—6.
[3] Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R. The locked-in syndrome: a syndrome looking for a therapy. Brain Inj 2002;16:555—69.
[4] Giacino JT, Hirsch J, Schiff N, Laureys S. Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. Arch Phys Med Rehabil 2006;87:S67—76.
[5] Laureys S, Giacino JT, Schiff ND, Schabus M, Owen AM. How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? Curr Opin Neurol 2006;19:520—7.
[6] Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3:537—46.
[7] Laureys S, Perrin F, Schnakers C, Boly M, Majerus S. Residual cognitive function in comatose, vegetative and minimally conscious states. Curr Opin Neurol 2005;18:726—33.
[8] Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: Davis, FA; 1983.
[9] Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet 1972;1:734—7.
[10] Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349—53.
[11] Laureys S. 43. Eyes open, brain shut: the vegetative state. Sci Am 2007;4:32—7.
[12] Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res 2005;150:495—511.
[13] Zeman A. Consciousness. Brain 2001;124(Pt 7):1263—89.
[14] Zeman A. What in the world is consciousness? In: Laureys S, editor. The boundaries of consciousness: neurobiology and neuropathology. Amsterdam: Elsevier Press; 2005. p. 1—10.
[15] Laureys S, Perrin F, Faymonville ME, Schnakers C, Boly M, et al. Cerebral processing in the minimally conscious state. Neurology 2004;63:916—8.
[16] Bindemann M, Burton AM, Jenkins R. Capacity limits for face processing. Cognition 2005;98:177—97.
[17] Bredart S, Delchambre M, Laureys S. One's own face is hard to ignore. Q J Exp Psychol 2006;59:46—52.
[18] Schnakers C, Majerus S, Laureys S. Diagnosis and investigation of altered states of consciousness. Reanimation 2004;13:368—75.
[19] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81—4.
[20] Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. Ann Neurol 2005;58:585—93.

[21] Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020—9.

[22] Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL. 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: 408—16.

[23] Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. Science 1965;150:1187—8.

[24] Berlad I, Pratt H. P300 in response to the subject's own name. Electroencephalogr Clin Neurophysiol 1995;96(5):472—4.

[25] Perrin F, Schnakers C, Schabus M, Degueldre C, Goldman S, Bredart S, et al. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol 2006;63:562—9.

[26] Signorino M, D'Acunto S, Angeleri F, Pietropaoli P. Eliciting P300 in comatose patients. Lancet 1995;345:255—6.

[27] Mutschler V, Chaumeil CG, Marcoux L, Wioland N, Tempe JD, Kurtz D. Auditory P300 in subjects in a post-anoxic coma. Preliminary data. Neurophysiol Clin 1996;26:158—63.

[28] Holeckova I, Fischer C, Giard MH, Delpuech C, Morlet D. Brain responses to a subject's own name uttered by a familiar voice. Brain Res 2006;1082:142—52.

[29] Brazdil M, Rektor I, Daniel P, Dufek M, Jurak P. Intracerebral event-related potentials to subthreshold target stimuli. Clin Neurophysiol 2001;112:650—61.

[30] Vogeley K, Bussfeld P, Newen A, Herrmann S, Happe F, Falkai P, et al. Mind reading: neural mechanisms of theory of mind and self-perspective. Neuroimage 2001;14:170—81.

[31] Kjaer TW, Nowak M, Lou HC. Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. Neuroimage 2002;17:1080—6.

[32] Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, et al. Remembering the past: two facets of episodic memory explored with positron emission tomography. Am J Psychiatry 1995;152:1576—85.

[33] Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 2000;9:207—31.

[34] Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage 1999;9:377—82.

[35] Maquet P, Faymonville ME, Degueldre C, Delfiore G, Franck G, Luxen A, et al. Functional neuroanatomy of hypnotic state. Biol Psychiatry 1999;45:327—33.

[36] Kaisti KK, Metsahonkala L, Teras M, Oikonen V, Aalto S, Jaaskelainen S, et al. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 2002;96:1358—70.

[37] Schiff ND, Rodriguez-Moreno D, Kamal A, Kim KH, Giacino JT, Plum F, et al. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 2005;64:514—23.

[38] Di HB, Yu SM, Weng XC, Laureys S, Yu D, Li JQ, et al. Cerebral response to patient's own name in the vegetative and minimally conscious states. Neurology 2007;68:895—9.

[39] Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006;313:1402.

Locked-in syndrome et états de conscience altérée : comment détecter la conscience ?

Locked-in syndrome and disorders of consciousness: how to detect consciousness?

A. Vanhaudenhuyse [1], M-A. Bruno [1], C. Schnakers [1], M. Boly [1], P. Boveroux [2], G. Moonen [3], F. Perrin [4], F. Pellas [5], K-H. Pantke [6], S. Laureys [3]

[1] Coma Science Group, Cyclotron Research Centre, University of Liège, Sart-Tilman B30, 4000 Liège, Belgium

[2] Coma Science Group, Cyclotron Research Centre and Department of Anesthesiology Neurology, University of Liège, Sart-Tilman B30, 4000 Liège, Belgium

[3] Coma Science Group, Cyclotron Research Centre and Department of Neurology, University of Liège, Sart-Tilman B30, 4000 Liège, Belgium

[4] UMR5020 « Neurosciences sensorielles, comportement, cognition », Université Claude Bernard Lyon 1 69366 Lyon, France

[5] Neurorehabilitation Medicine, Hôpital Caremeau, CHU Nîmes, 30029 Nîmes Cedex, France

[6] German Association Locked In Syndrome LIS e.V., Evangelischen Krankenhaus Köningin Elisabeth Herzberge gGmbh, Haus 30, Herzbergstrasse 79, 10365 Berlin, Germany

Abstract:

Non-communicative post-comatose patients may be considered as vegetative while actually being conscious. Such diagnostic error could be avoided by using objective ways to detect consciousness. We will here review electrophysiological and functional neuroimaging methods of use in the differential diagnosis of the locked-in syndrome. Cognitive evoked-potentials can disentangle vegetative from locked-in syndrome patients. Positron emission tomography studies permit to quantify residual cerebral activity in resting conditions. Finally, so-called active paradigms where the patient is asked to perform mental imagery tasks during functional MRI scanning may permit to identify consciousness in otherwise non-responsive coma survivors.

Introduction

Je suis ce que l'on surnomme vulgairement un légume. A trois détails près non négligeables : j'ai toute ma tête, je sens les mains qui me touchent, et j'ai découvert que mes paupières n'étaient pas seulement deux peaux qui protègent les globes oculaires et qui accueillent des fards multicolores. Laetitia Bohn-Derrien [4].

Depuis plus de 50 ans, les progrès en médecine ont considérablement augmenté le nombre de patients survivant à un accident cérébral sévère. Pour le clinicien, détecter un patient locked-in reste difficile. En effet, la conscience est un phénomène subjectif et nous sommes limités à interpréter nos observations lorsque nous travaillons avec des patients non-communicatifs. L'enjeu actuel est de déterminer si l'absence de signes manifestes de conscience est la preuve de l'inconscience de ces patients. Plusieurs récits, comme celui de Julia Tavalaro par exemple, témoignent de cette problématique. Pendant six ans, Julia fut considérée comme un « légume » et vécut un enfer au cours duquel elle a dû se battre pour se faire entendre [29]. Malheureusement, ces témoignages ne sont pas rares et beaucoup de patients sont diagnostiqués en état végétatif alors qu'ils sont en réalité conscients. Les limites évidentes des observations comportementales doivent nous inciter à chercher des marqueurs objectifs de la conscience tels que l'électroencéphalographie et les potentiels évoqués ainsi que la neuroimagerie fonctionnelle. Dans cette revue, nous définirons les différentes entités cliniques pouvant être rencontrées chez des patients sévèrement cérébrolésés ainsi que l'étiologie du locked-in syndrome et les erreurs diagnostiques fréquentes pour cette pathologie. Ensuite, nous passerons en revue les différentes techniques nous offrant la possibilité de tester objectivement la conscience chez des patients qui sont incapables de la démontrer clairement.

Du coma au locked-in syndrome : définitions, pronostic et diagnostic

Après un accident cérébral, certains patients se rétablissent rapidement, tandis que d'autres traversent différents états tels que le coma, l'état végétatif (EV), l'état de conscience minimale (ECM) ou le locked-in syndrome (LIS). D'autres patients peuvent également être diagnostiqués en état de mort cérébrale, lequel est défini comme la perte irréversible de toutes fonctions cérébrales. Quant au coma, il est caractérisé par une absence d'ouverture des yeux, même lors d'une stimulation douloureuse [26]. Un patient en EV, chez qui seuls des comportements réflexes sont observables, ouvre les yeux et fait preuve d’un cycle veille-sommeil préservé [30]. Certains patients évoluent de l’EV vers l’ECM. Les manifestations de conscience chez un patient en ECM se traduisent par des comportements reproductibles et soutenus, bien qu’éventuellement fluctuants, tels que des réponses adéquates à une commande motrice, une poursuite visuelle soutenue et/ou une localisation de stimulations nociceptives et/ou auditives [8].

Dans les différents états décrits ci-dessus, la conscience des patients est clairement altérée. Le locked-in syndrome (LIS) doit absolument être considéré comme une pathologie à part des états de conscience altérée. En effet, le locked-in syndrome est définit comme « un tableau clinique observé chez un patient conscient, associant : (I) la présence d’une ouverture continue des paupières (en l’absence de ptosis bilatéral, dans lequel cas l’examinateur devra ouvrir manuellement les yeux du patient), (II) des capacités cognitives relativement intactes, (III) une aphonie ou une hypophonie sévère, (IV) une quadriplégie ou une quadriparésie et (V) une communication basée principalement sur les mouvements oculo-palpébraux [1]. Cette pathologie peut être divisée en trois catégories selon l’étendue du handicap moteur et verbal [3]. Le LIS classique est caractérisé par une immobilité totale à l’exception du mouvement vertical des yeux et du clignement des paupières. Le LIS incomplet bénéficie de quelques reliquats de motricité volontaire. Le LIS complet implique une immobilité complète, s’étendant à l’ensemble de la motricité oculaire.

Les causes les plus fréquentes du LIS sont l’occlusion de l’artère basilaire et l’hémorragie pontine [Tableau I]. Cependant, d’autres étiologies ne doivent pas être exclues. Elles comprennent : 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. Le LIS complet est également observé en fin de sclérose latérale amyotrophique. D’autres cas de LIS, plus rares, sont parfois causés par une hémorragie subarachnoïdales avec des spasmes de l’artère basilaire, une tumeur du tronc cérébral, une myélinolyse centro-pontine, une encéphalite, un abcès de la protubérance, une intoxication au niveau du tronc cérébral, une réaction à un vaccin ou une hypoglycémie prolongée. Des cas de LIS complets temporaires ont été signalés après un syndrome de Guillain Barré ou des polyneurophaties post-infectieuses sévères. Des cas de LIS réversibles peuvent également être observés lorsque le patient reçoit un curare avec une dose insuffisante d'anesthésiants (pour des revues, voir [5, 16]).

Tableau I : Etiologie du LIS en Europe et aux Etats-Unis (EU). Adapté de Bruno et al. [5]

Références	Age à l'accident (moyenne)	Pays	Etiologie vasculaire (%)
Base de données de l'ALIS	45	France	86
Pantke et al. (non publié)	39	Allemagne	90
Leon-Carrion et al. [18]	47	Espagne	86
Casanova et al. [7]	45	Italie	79
Patterson et Grabois [24]	52	EU	60
Katz et al. [11]	34	EU	52
Richard et al. [28]	45	EU	91

Détecter un patient LIS reste une tâche difficile. En effet, le patient peut être considéré comme étant dans le coma ou en EV alors qu'il est complètement conscient. Cette difficulté à déceler des signes de conscience chez des patients cérébrolésés peut s'expliquer par les déficits moteurs ainsi que la fluctuation du niveau de vigilance (pour une revue, voir [20]). Les mouvements volontaires des yeux et/ou le clignement des paupières peuvent être, à tort, interprétés comme des mouvements réflexes chez des patients souffrant d'anarthrie, qui classiquement présentent une posture de « décérébration » (c'est-à-dire des réflexes d'extension stéréotypés). Une étude réalisée en collaboration avec l'Association Française pour le Locked-In Syndrome (ALIS) a démontré que dans 55% des cas, c'était un proche et pas un médecin (23% des cas) qui découvrait que le patient était conscient et capable de communiquer grâce à des mouvements des yeux. En moyenne, le temps écoulé entre l'accident cérébral et le diagnostic du LIS était de 78 jours [9].

Comment différencier un LIS d'un état de conscience altérée grâce à des marqueurs objectifs ?

Electrophysiologie

La première analyse d'enregistrements électroencéphalographiques (EEG), réalisée sur huit patients atteints du LIS, a démontré que les tracés étaient normaux ou légèrement plus lents pour sept patients et que la réactivité aux stimuli externes était préservée chez tous ces patients [21]. Plus tard, Bassetti et al. confirmaient ces résultats sur six patients LIS chez qui ils démontrèrent une activité alpha réactive et normalement distribuée [2]. Cependant, certaines études mettent en évidence un EEG non réactif chez des patients LIS. En effet, dans leur revue de la littérature, Patterson et Grabois ont noté un ralentissement des guides temporaux et frontaux ainsi qu'un ralentissement diffus du signal EEG chez 55% des patients [24]. Par ailleurs, Jacome et Morilla-Pastro ont observé un rythme alpha non réactif aux stimuli mutlimodaux particulièrement chez des patients dont le LIS résultait d'un accident vasculaire cérébral [10]. Gütling et al. ont également observé un tracé alpha non réactif chez trois patients LIS, dont un LIS permanent [9]. 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 LIS 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 LIS.

Une autre technique, celle des potentiels évoqués (*event-related potentials* – ERPs), méthode dérivée de l'EEG, permet d'enregistrer l'activité électrique spontanée du cerveau afin d'identifier le niveau de vigilance et de détecter des anomalies cérébrales fonctionnelles. Alors que l'EEG ne permet pas de quantifier les changements minimes induits par des activités sensorielles, motrices et cognitives ; les ERPs permettent de détecter des variations fonctionnelles plus subtiles. Les ERPs obtenus suite à une stimulation sensorielle, reflètent le parcours temporel de l'information, des structures réceptives périphériques jusqu'aux cortex associatifs. Il existe deux types d'ERPs. Les ERPs de courte latence, appelés aussi composantes ERPs exogènes (avec une latence de 0 à 100 ms), correspondent à l'activation des voies ascendantes vers le cortex primaire. Les ERPs cognitifs, ou composantes ERPs endogènes (apparaissant après 100 ms), sont le reflet d'une activité tant au niveau des structures corticales que sous-corticales, incluant notamment les aires associatives. Tandis que les ERPs de courte latence dépendent des propriétés physiques du stimulus, les ERPs cognitifs sont influencés par le contenu du stimulus ainsi que par les conditions expérimentales et le niveau d'éveil et d'attention du sujet (pour une revue, voir [32]).

Les ERPs de courte latence sont régulièrement utilisés chez les patients dans le coma afin de savoir s'ils vont ou non évoluer. L'absence d'ERPs somatosensoriels (*somatosensorial evoked-potentials* – SEPs), obtenus grâce à une stimulation électrique du nerf médian, et d'ERPs auditifs chez un patient en état de conscience altérée est étroitement liée à un mauvais pronostic ; alors que leur présence n'est pas une condition *sine qua non* de bonne récupération. De plus, les SEPs ne semblent pas être un indicateur fiable de conscience chez ces patients, comme l'ont démontré plusieurs études [2, 31]. Nous ne pouvons donc pas les utiliser pour détecter un LIS. Toutefois, certains travaux montrent que les ERPs moteurs (*motor evoked-potentials* – MEPs) pourraient être intéressants pour statuer sur la récupération des patients atteints d'un LIS. La présence de MEPs chez les patients LIS au stade aigu pourrait être considérée comme un indice de récupération tandis que leur absence ne peut pas être interprétée comme une preuve de non-récupération [2].

Si les ERPs de courte latence sont utiles pour prédire la sortie d'un coma, ils le sont moins pour prédire la récupération des patients. Par ailleurs, leur utilisation offre uniquement une information sur l'intégrité des voies ascendantes. Les ERPs cognitifs, quant à eux, permettront de statuer sur la préservation des fonctions cognitives des patients. Le problème actuel est que les résultats concernant ces ERPs sont très hétérogènes. Cependant, nous pouvons retenir de la littérature que les ERPs cognitifs semblent avoir une bonne valeur prédictive de la récupération, en particulier les ondes MMN et P300. Ces potentiels peuvent réellement aider le clinicien à estimer les fonctions résiduelles chez les patients en état de conscience altérée (pour une revue, voir [32]). Chez les patients LIS, les ERPs cognitifs peuvent jouer un rôle important dans le diagnostic. Dans leur étude, Onofrj et al. ont démontré qu'il était possible d'enregistrer des ERPs cognitifs chez des patients LIS peu de temps après leur accident [22]. Ils ont également montré leur utilité lors de l'évaluation de l'état de conscience chez des patients LIS complets dont la pathologie était causée par une sclérose latérale amyotrophique en phase terminale [12] et un syndrome de Guillain-Barré [27]. Quant à l'onde P3 en réponse au propre prénom, très étudiée ces dernières années, nous avons démontré qu'elle ne permettait pas de différencier des patients LIS des patients en EV [25]. En effet, cette onde est observée chez tous les patients LIS, fait non surprenant puisque leur capacités cognitives sont intactes, mais également chez tous les patients en ECM et même chez certains patients en EV [Figure I].

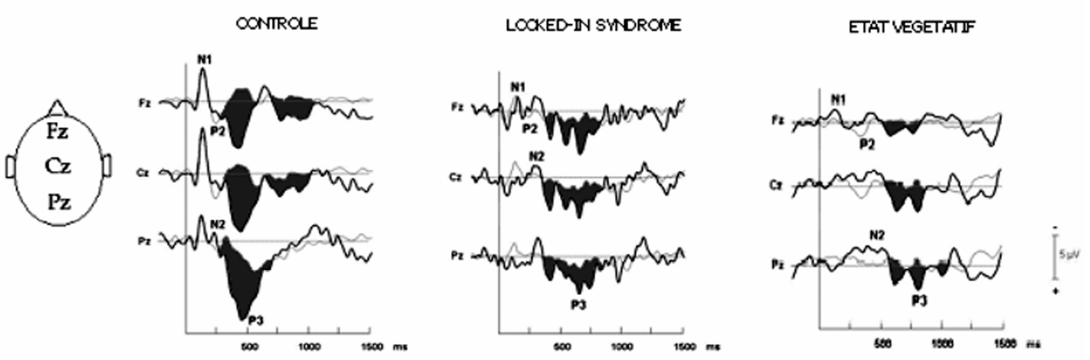


Figure I : L’onde P300 ne permet pas de différencier les patients en locked-in syndrome (LIS) des patients en état végétatif (EV). Cette onde (en gris sur le graphique) est présente chez tous les patients LIS ainsi que chez certains patients en EV. Adapté de Perrin et al. [25]

Neuroimagerie fonctionnelle

A l’aide de la tomographie à émission de positons (TEP), nous avons pu montrer que l’activité métabolique cérébrale globale diminuait de plus de la moitié chez les patients en EV comparés aux sujets normaux [13], tout comme cela peut être observé pendant le sommeil lent profond ou au cours de l’anesthésie générale. Cependant, cette diminution globale ne semble pas être une explication de l’absence de conscience chez les patients végétatifs puisque leur récupération ne s’accompagne pas nécessairement d’une modification de l’activité métabolique cérébrale globale [13, 14]. En effet, l’EV est également caractérisé par une diminution focale du métabolisme comprenant les aires associatives polymodales. Plus explicitement, cet état peut être défini comme un syndrome de déconnexion des aires préfrontales et pariétales avec le thalamus. Une région semble jouer un rôle clef dans la différenciation EV – ECM : le cortex pariétal médian (le précuneus) et le cortex cingulaire postérieur adjacent. Ces deux aires cérébrales sont celles dont le métabolisme est le plus altéré dans l’EV alors que leur activité est significativement plus importante dans l’ECM et encore davantage dans le LIS [15, 19]. De plus, nous n’avons observé aucune diminution significative du métabolisme cérébral chez les patients LIS par rapport à celle des sujets contrôles [17].

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 LIS [18]. Une hyperactivité significative de l’amygdale est également observée chez les patients LIS 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 [6]. Dès lors, nous pouvons supposer que l’augmentation de l’activité de la région amygdalienne observée chez les patients LIS en phase initiale est liée à la situation terrifiante qui est la leur, à savoir être conscient mais prisonnier d’un corps inerte et incapable de communiquer. Il est donc nécessaire de diagnostiquer correctement et le plus rapidement possible le LIS afin d’adapter la prise en charge thérapeutique aussi bien médicamenteuse que comportementale à cette situation terrible et très forte en émotion. Enfin, grâce à l’Imagerie par Résonance Magnétique fonctionnelle (IRMf), nous avons observé que la conscience pouvait être détectée par la manifestation d’activations cérébrales similaires à celles observées chez des sujets contrôles lors de tâches d’imagination motrice [23]. Si un patient, manifestement inconscient suite aux diverses observations comportementales, démontre une activité cérébrale identique à un groupe contrôle, nous pouvons nous permettre d’en conclure que ce patient entend, comprend et réalise la tâche qui lui a été demandée. Il est donc indubitablement conscient.

Conclusion

La recherche de marqueurs objectifs de conscience n’est pas encore terminée. Néanmoins, les travaux déjà réalisés en ce domaine nous offrent la possibilité de détecter rapidement la présence d’une conscience chez des patients incapables d’en faire la démonstration. La technique des potentiels évoqués cognitifs est relativement facile à introduire dans la pratique clinique. Elle serait d’un grand secours pour détecter un locked-in syndrome dès les premiers instants après la sortie d’un coma. Si la neuroimagerie fonctionnelle est plus onéreuse, elle n’en reste pas moins très sensible. En effet, nous avons démontré que l’emploi d’un paradigme actif en IRMf permettait de vérifier si un patient, en apparence inconscient, était capable d’obéir à des commandes verbales [23]. Si un patient démontre cette capacité à répondre à une commande, capacité vérifiée par des activations cérébrales significatives, en aucun cas nous ne pourrons nier la présence d’une conscience chez cette personne. Dès lors, si les observations comportementales ne nous semblent pas suffisantes pour émettre un diagnostic sûr, nous ne devrions pas hésiter à faire appel à des techniques telles que les ERPs et l’IRMf.

Références

1. American Congress of Rehabilitation Medicine: Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Arch Phys Med Rehabil* 1995, 76:205-209.
2. Bassetti C, Mathis J, Hess CW: Multimodal electrophysiological studies including motor evoked potentials in patients with locked-in syndrome: report of six patients. *J Neurol Neurosurg Psychiatry* 1994, 57(11):1403-1406.
3. Bauer G, Gerstenbrand F, Rumpl E: Varieties of the locked-in syndrome. *J Neurol* 1979, 221(2):77-91.
4. Bohn-Derrien L: Je parle. L'extraordinaire retour à la vie d'un locked-in syndrom. Paris: JC Lattès; 2005.
5. Bruno M, Pellas F, Schnakers C, Van Eeckhout P, Pantke K, Damas F, Faymonville M, Moonen G, Goldman S, Steven L: Le Locked-In syndrome : la conscience emmurée. *Revue de Neurologie* 2007, Submitted.
6. Calder AJ, Lawrence AD, Young AW: Neuropsychology of fear and loathing. *Nat Rev Neurosci* 2001, 2(5):352-363.
7. Casanova E, Lazzari RE, Lotta S, Mazzucchi A: Locked-in syndrome: improvement in the prognosis after an early intensive multidisciplinary rehabilitation. *Arch Phys Med Rehabil* 2003, 84(6):862-867.
8. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD *et al*: The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002, 58(3):349-353.
9. Gutling E, Isenmann S, Wichmann W: Electrophysiology in the locked-in-syndrome. *Neurology* 1996, 46(4):1092-1101.
10. Jacome DE, Morilla-Pastor D: Unreactive EEG: pattern in locked-in syndrome. *Clin Electroencephalogr* 1990, 21(1):31-36.
11. Katz RT, Haig AJ, Clark BB, DiPaola RJ: Long-term survival, prognosis, and life-care planning for 29 patients with chronic locked-in syndrome. *Arch Phys Med Rehabil* 1992, 73(5):403-408.
12. Kotchoubey B, Lang S, Winter S, Birbaumer N: Cognitive processing in completely paralyzed patients with amyotrophic lateral sclerosis. *Eur J Neurol* 2003, 10(5):551-558.

13. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, Franck G, Maquet P: Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage* 1999, 9(4):377-382.
14. Laureys S, Lemaire C, Maquet P, Phillips C, Franck G: Cerebral metabolism during vegetative state and after recovery to consciousness. *J Neurol Neurosurg Psychiatry* 1999, 67(1):121.
15. Laureys S, Owen AM, Schiff ND: Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 2004, 3(9):537-546.
16. Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, Berre J, Faymonville ME, Pantke KH, Damas F *et al*: The locked-in syndrome : what is it like to be conscious but paralyzed and voiceless? *Prog Brain Res* 2005, 150:495-511.
17. Laureys S, van Eeckhout P, Ferring M, Faymonville M, Mavroudakis N, Berre J, Van Bogaert P, Pellas F, Cornu P, Luxen A *et al*: Brain function in acute and chronic locked-in syndrome. *Presented at the 9th Annual Meeting of the Organisation for Human Brain Mapping (OHBM), June 18-22, 2003, NY, USA, NeuroImage CD ROM Volume 19, Issue 2, Supplement 1* 2003.
18. Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R, Perez-Santamaria FJ: The locked-in syndrome: a syndrome looking for a therapy. *Brain Inj* 2002, 16(7):571-582.
19. Levy DE, Sidtis JJ, Rottenberg DA, Jarden JO, Strother SC, Dhawan V, Ginos JZ, Tramo MJ, Evans AC, Plum F: Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann Neurol* 1987, 22(6):673-682.
20. Majerus S, Gill-Thwaites H, Andrews K, Laureys S: Behavioral evaluation of consciousness in severe brain damage. *Prog Brain Res* 2005, 150:397-413.
21. Markand ON: Eectroencephalogram in "locked-in" syndrome. *Electroencephalogr Clin Neurophysiol* 1976, 40(5):529-534.
22. Onofrj M, Thomas A, Paci C, Scesi M, Tombari R: Event related potentials recorded in patients with locked-in syndrome. *J Neurol Neurosurg Psychiatry* 1997, 63(6):759-764.
23. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD: Detecting awareness in the vegetative state. *Science* 2006, 313(5792):1402.

24. Patterson JR, Grabois M: Locked-in syndrome: a review of 139 cases. *Stroke* 1986, 17(4):758-764.

25. Perrin F, Schnakers C, Degueldre C, Schabus M, Goldman S, Brédart S, Faymonville M, Lamy M, Moonen G, Luxen A *et al*: Brain response to one's own name in vegetative state, minimally conscious state and locked-in syndrome. *Archives of Neurology* 2006, 63(4)(562-9).

26. Plum F, Posner JB: The diagnosis of stupor and coma. *Philadelphia: Davis,FA* 1983.

27. Ragazzoni A, Grippo A, Tozzi F, Zaccara G: Event-related potentials in patients with total locked-in state due to fulminant Guillain-Barre syndrome. *Int J Psychophysiol* 2000, 37(1):99-109.

28. Richard I, Pereon Y, Guiheneu P, Nogues B, Perrouin-Verbe B, Mathe JF: Persistence of distal motor control in the locked in syndrome. Review of 11 patients. *Paraplegia* 1995, 33(11):640-646.

29. Tavalaro J, Tayson R: Look up for yes. New York, NY: Kodansha America, Inc.; 1997.

30. The Multi-Society Task Force on PVS: Medical aspects of the persistent vegetative state (1). *N Engl J Med* 1994, 330(21):1499-1508.

31. Towle VL, Maselli R, Bernstein LP, Spire JP: Electrophysiologic studies on locked-in patients: heterogeneity of findings. *Electroencephalogr Clin Neurophysiol* 1989, 73(5):419-426.

32. Vanhaudenhuyse A, Laureys S, Perrin F: Cognitive event-related potentials in comatose and post-comatose states. *Neurocritical Care* 2007, in press.

BMC Neurology

Research article

Open Access

Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment

Caroline Schnakers[1], Audrey Vanhaudenhuyse[1], Joseph Giacino[2], Manfredi Ventura[3], Melanie Boly[1,4], Steve Majerus[5], Gustave Moonen[4] and Steven Laureys*[1,4]

Address: [1]Coma Science Group, Cyclotron Research Center, University of Liege, Belgium, [2]New Jersey Neuroscience Institute, Edison, NJ, USA, [3]CTR Neurorehabilitation Centre, Université Libre de Bruxelles, Brussels, Belgium, [4]Department of Neurology, Centre Hospitalier Universitaire Sart Tilman, University of Liege, Belgium and [5]Department of Cognitive Sciences, Experimental Psychology and Cognitive Neuroscience Research Unit-URPENC, University of Liege, Belgium

Email: Caroline Schnakers - c.schnakers@hotmail.com; Audrey Vanhaudenhuyse - avanhaudenhuyse@student.ulg.ac.be; Joseph Giacino - JGiacino@solarishs.org; Manfredi Ventura - manfredi.ventura@ctrbxl.be; Melanie Boly - mboly@student.ulg.ac.be; Steve Majerus - smajerus@ulg.ac.be; Gustave Moonen - G.Moonen@ulg.ac.be; Steven Laureys* - steven.laureys@ulg.ac.be

* Corresponding author

Published: 21 July 2009

BMC Neurology 2009, **9**:35 doi:10.1186/1471-2377-9-35

Received: 10 February 2009
Accepted: 21 July 2009

This article is available from: http://www.biomedcentral.com/1471-2377/9/35

© 2009 Schnakers et al; licensee BioMed Central Ltd.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Previously published studies have reported that up to 43% of patients with disorders of consciousness are erroneously assigned a diagnosis of vegetative state (VS). However, no recent studies have investigated the accuracy of this grave clinical diagnosis. In this study, we compared consensus-based diagnoses of VS and MCS to those based on a well-established standardized neurobehavioral rating scale, the JFK Coma Recovery Scale-Revised (CRS-R).

Methods: We prospectively followed 103 patients (55 ± 19 years) with mixed etiologies and compared the clinical consensus diagnosis provided by the physician on the basis of the medical staff's daily observations to diagnoses derived from CRS-R assessments performed by research staff. All patients were assigned a diagnosis of 'VS', 'MCS' or 'uncertain diagnosis.'

Results: Of the 44 patients diagnosed with VS based on the clinical consensus of the medical team, 18 (41%) were found to be in MCS following standardized assessment with the CRS-R. In the 41 patients with a consensus diagnosis of MCS, 4 (10%) had emerged from MCS, according to the CRS-R. We also found that the majority of patients assigned an uncertain diagnosis by clinical consensus (89%) were in MCS based on CRS-R findings.

Conclusion: Despite the importance of diagnostic accuracy, the rate of misdiagnosis of VS has not substantially changed in the past 15 years. Standardized neurobehavioral assessment is a more sensitive means of establishing differential diagnosis in patients with disorders of consciousness when compared to diagnoses determined by clinical consensus.

Background

Differentiating the vegetative (VS) from minimally conscious state (MCS) is often one of the most challenging tasks facing clinicians involved in the care of patients with disorders of consciousness (DOC). Whereas VS is characterized by the return of arousal without signs of awareness [1], MCS is defined by the presence of inconsistent but reproducible goal-directed behaviors (e.g. response to command, verbalizations, visual pursuit, etc.) [2]. Behavioral assessment remains the "gold standard" for detecting signs of consciousness and, hence, for determining diagnosis [3]. However, behavioral assessment is complicated by the presence of motor impairment, tracheotomy, fluctuating arousal level or ambiguous and rapidly habituating responses [4]. Previous studies have shown that 37 to 43% of patients diagnosed with VS demonstrated signs of awareness [5,6]. Misdiagnosis can lead to grave consequences, especially in end-of-life decision-making [7]. Contrary to patients in VS, those in MCS retain some capacity for cognitive processing and activate similar brain networks relatives to controls following painful stimulation; suggesting that they can experience pain [8,9]. Moreover, the prognosis of patients in MCS is significantly more favorable relative to those in VS [10]. End-of-life decisions, therefore, are likely to be influenced by whether one is diagnosed with MCS or VS. In 2002, criteria were proposed to characterize MCS and identify behaviors that signal emergence from this state [2]. In view of the availability of the MCS criteria, the incidence of misdiagnosis of VS should be lower than the rates reported before these criteria were established [11]. However, no recent studies have investigated the accuracy of this grave clinical diagnosis. Over the last 15 years, specialized neurobehavioral rating scales have been developed to provide a reliable and valid means of detecting signs of consciousness. There are significant differences among these scales, however, with respect to diagnostic sensitivity [3]. The Coma Recovery Scale-Revised (CRS-R) was developed specifically to differentiate MCS from VS [12]. We recently showed that the proportion of patients diagnosed with MCS by the CRS-R was significantly higher as compared to other neurobehavioral scales such as the Glasgow Coma Scale [13], the Full Outline of UnResponsiveness [14] and the Wessex Head Injury Matrix [15]. These results suggest that the type of assessment tool used is crucial to accurate diagnosis [16,17]. In this study, we compared consensus-based diagnoses of VS and MCS to those based on the CRS-R, a well-established standardized neurobehavioral rating scale.

Methods

Participating centers were intensive care and neurology units as well as neurorehabilitation centers, part of the Belgian federal network for care of patients in VS and MCS. All the patients included in this study were recruited according to pre-arranged inclusion/exclusion criteria. Inclusion criteria were a) severe acquired brain injury causing disturbance in consciousness, b) no neuromuscular function blockers and no sedation within the prior 24 hours and c) periods of eye opening (indicating preserved sleep-wake cycles and emergence from coma). Exclusion criteria were a) documented history of prior brain injury, b) premorbid history of developmental, psychiatric or neurologic illness resulting in documented functional disabilities up to time of the injury and c) acute illness. Additionally, the following clinical information was collected from the medical file of each patient: age, gender, past medical history, medication, time since onset and etiology.

We used a standardized neurobehavioral assessment scale to determine patients' level of consciousness: the Coma Recovery Scale-Revised (CRS-R) [12]. The CRS-R assesses auditory, visual, verbal and motor functions as well as communication and arousal level. The total score ranges between 0 (worst) and 23 (best). The CRS-R has shown superior performance in detecting VS and MCS compared to other scales [12,16,17]. Post-comatose patients were assessed once with the CRS-R by experienced raters (CS or AV). Relying on the Aspen criteria [2], we operationalized the definitions of VS, MCS and emergence from MCS using the items on the scale that were designed for this purpose. CRS-R-derived diagnostic criteria are mentioned in Table 1. We compared the diagnosis derived from the CRS-R assessments performed by the research team (CS or AV) to the clinical consensus diagnosis. The clinical consensus diagnosis was based on daily behavioral observations and included observations made within the last 24 hours by a clinical team comprised of physicians, psychologists, speech therapists, occupational therapists, physiotherapists and nurses. The research team was not involved in the clinical consensus diagnoses. The physicians recorded the clinical consensus diagnosis according to the observations reported by each member of the clinical team during structured but also unstructured team meetings and, in all cases, communicated this diagnosis to the research team prior to conducting the CRS-R assessment. The research team was hence not masked to the clinical consensus diagnoses. When all the clinical staff agreed,

Table 1: CRS-R's diagnostic criteria for vegetative (VS) and minimally conscious (MCS) states and emergence from MCS

VS	Auditory ≤ 2 *AND* Visual ≤ 1 *AND* Motor ≤ 2 *AND* Oromotor/Verbal ≤ 2 *AND* Communication = 0 *AND* Arousal ≤ 2
MCS	Auditory = 3–4 *OR* Visual = 2–5 *OR* Motor = 3–5 *OR* Oromotor/Verbal = 3 *OR* Communication = 1
Emergence from MCS	Motor = 6 *OR* Communication = 2

diagnosis was deemed VS or MCS. When even one person disagreed, the diagnosis was deemed 'uncertain'. Patients thought to have emerged from MCS based on consensus diagnosis were not assessed on the CRS-R. All patients were assessed once by the research team and were assigned a diagnosis of VS, MCS or emerged from MCS. Differences in diagnosis relative to length of time post-injury (acute vs. chronic) and etiology (traumatic vs. non-traumatic) were assessed using Chi square test, thresholded for significance at $p < 0.05$. The study was approved by the Ethics Committee of the University of Liège. Informed consent was obtained from each patient's legal surrogate.

Results

The data were collected between October 2005 and January 2007. We enrolled 103 patients in this study (74 in acute care and neurology units and 29 in neurorehabilitation centers). There were 71 males (69%) and mean age was 55 ± 19 years. Forty-six patients (45%) were in the acute recovery period (mean 12 ± 7 days) and 57 were in the chronic stage (55%) (mean 22 ± 52 months) [16]. The following etiologies were included [9]: traumatic head injury (n = 39), postanoxic-ischemic encephalopathy (n = 31), ischemic or hemorrhagic stroke (n = 16), aneurysmal subarachnoid hemorrhage (n = 6), metabolic encephalopathy (n = 5) and miscellaneous acute neurological conditions (n = 6).

Of the 44 patients with a clinical consensus diagnosis of VS, the CRS-R detected signs of awareness in 18 patients (41%). Misdiagnosis was greater for chronic (14 out of 29; 48%) than for acute patients (4 out of 15; 27%) ($Chi^2 = 7$; $p < .01$; CI (95%) = 39.55 to 60.45). Behavioral signs of consciousness detected by the CRS-R in patients misdiagnosed by clinical consensus primarily included purposeful eye movements (visual fixation: n = 3; visual pursuit: n = 5). In patients assigned a clinical consensus diagnosis of MCS (n = 41), 10% (n = 4) met criteria for emergence from MCS. All four of the patients found to have emerged from MCS were in the chronic stage. Finally, among the 18 patients with an uncertain clinical consensus diagnosis, 16 manifested signs of consciousness (89%; 8 acute and 8 chronic) when examined with the CRS-R. The clinical signs most often encountered in the latter patients were again purposeful eye movements (visual fixation, n = 4; pursuit, n = 2) (see Table 2). Finally, we observed no significant difference in diagnostic accuracy when traumatic cases were compared with non-traumatic cases.

Discussion

In this geographically-diverse sample drawn from a Belgian federal network of brain injury treatment centers, the rate of misdiagnosis of VS (41%) is roughly equivalent to rates reported in the U.S. and U.K. before the criteria for MCS were published [5,6]. Misdiagnosis occurred most often as the result of failure to detect purposeful eye movements (i.e., visual fixation and pursuit), in line with previous studies [5]. Moreover, our study suggests that the majority of cases with an uncertain diagnosis are in MCS (89%), not in VS. Finally, a false negative diagnosis of MCS was noted in 10% of cases that had emerged from this condition.

Table 2: Behavioral signs of consciousness found in patients misdiagnosed with VS and MCS or with uncertain clinical consensus diagnosis.

Behavior	VS	MCS	Unsure of diagnosis
1 – response to verbal order	4	*	4
2 – purposeful eye movements	8	*	6
3 – automatic motor response	1	*	1
4 – pain localization	1	*	1
5 – several criteria for MCS	4	*	4
6 – communication	*	1	*
7 – functional object use	*	1	*
8 – several criteria for EMCS	*	2	*
Total	18	4	16

Notice: EMCS = emergence from MCS; * Non-appropriate; several criteria for MCS = presence of several criteria such as response to verbal order, purposeful eye movements, automatic motor response and/or pain localization; several criteria for EMCS = presence of communication and functional object use.

One could argue that the false negative consensus-based MCS diagnoses actually represent false positive CRS-R diagnoses of MCS. This possibility cannot be excluded but is also not easily resolved. As false positive errors increase, specificity decreases. However, in the context of a weak gold standard, false positives may not actually reflect diagnostic errors. If we consider the clinical consensus diagnosis as the gold standard, then false positive errors on the comparison measure (i.e., diagnosis of MCS) will result in lower specificity. Such false positive errors may, however, be due to the superior capacity of the comparison measure to detect the behavior of interest. In this case, the CRS-R, a standardized measure, captured more behavioral signs of consciousness relative to the collective impression of the medical team. One could also argue that there was a bias in favor of the research team's diagnostic accuracy as the researchers were not blind to the consensus diagnosis. The research team's knowledge of the clinical consensus diagnosis may hence have overestimated the sensitivity of CRS-R to detect signs of consciousness. However, the CRS-R requires replication of behavioral responses before scoring them as present (e.g., a response to verbal order is considered scoreable if the appropriate behavior is observed on 3 out of 4 trials) and, as such, decreases the risk of a false positive diagnosis. Future studies including blind assessment could be performed in order to comfort our results.

Spontaneous recovery is unlikely to explain our results as the clinical consensus diagnosis included behaviors observed by the medical staff within the prior 24 hours and was provided just before the CRS-R assessment. It is more likely that the examiners' reliance on unstructured bedside observations contributed to the high rate of misdiagnosis of VS patients. Indeed, it has been suggested that misdiagnosis is influenced by the use of a standardized behavioral tool [4]. In this study, we compared the accuracy of diagnoses based on standardized behavioral assessment using the CRS-R with consensus-based diagnoses established by the medical team following qualitative observations. Unlike traditional bedside assessment, the CRS-R guards against misdiagnosis by incorporating items that directly reflect the existing diagnostic criteria for MCS, and by operationalizing scoring criteria for the identification of behaviors associated with consciousness. Standardized assessment approaches may hence mitigate the tendency to miss signs of consciousness that may arise when the diagnosis is based solely on routine bedside examination. In cases with ambiguous behavioral findings, the failure to employ a standardized behavioral tool may increase the likelihood of misdiagnosis. Reliance on qualitative (versus standardized) assessment could also explain the higher rate of misdiagnosis observed for VS and MCS patients in both chronic and acute care settings. There is evidence to support this premise. Data regarding the use of a standardized behavioural scale were collected for each centre involved in this study. The behavioural scales' scores were not reported to the research team but were taken in account for the clinical consensus diagnosis. All 46 patients in the acute setting were evaluated with the Glasgow Coma Scale, a standardized assessment tool, and only 4 of these cases (10%) were misdiagnosed. In contrast, of the 57 chronic patients, 30 were not assessed using a standardized measure and 9 cases (30%) were misdiagnosed.

Finally, for uncertain diagnoses, we did not collect information on who disagreed and how frequently. While it would be helpful to know if uncertain diagnoses were due to the ambiguity of patient's responses or to the observational skills of the examiner, the aim of this study was to assess the misdiagnosis rate rather than explain the causes of misdiagnosis.

Conclusion

Despite the importance of diagnostic accuracy and advances in the past 15 years, the rate of misdiagnosis among patients with disorders of consciousness has not substantially changed. Although early detection of signs of consciousness is crucial not only for daily management (particularly, pain treatment), end-of-life decisions [7] and prognosis (i.e., patients in MCS have significantly more favorable outcomes as compared to those in VS [10]), clinicians should recognize that diagnoses established during the acute stage tend to be transitional and may change over time as the injury sequelae resolve. The results of this study suggest that the systematic use of a sensitive standardized neurobehavioral assessment scale may help decrease diagnostic error and limit diagnostic uncertainty. Future studies should investigate other factors influencing diagnostic accuracy.

List of abbreviations used

The list of abbreviations used is the following: CRS-R: (Coma Recovery Scale-Revised); VS: (Vegetative State); MCS: (Minimally Conscious State).

Competing interests

Dr Giacino participated in the development of the CRS-R and was involved in the review and discussion of the study results but did not participate in the study design, data collection or analyses.

Authors' contributions

CS made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data as well as in drafting the manuscript; AV was implied in collecting behavioural data, in the interpretation of data as well as in drafting the manuscript; JG gave critical revision of the manuscript for important intellectual content; MV, MB, SM and GM were involved in drafting the manuscript; SL made substantial contributions to design and supervised this study. All authors read and approved the final manuscript.

Acknowledgements

This research was supported by funds from the Belgian Federal Public Service for Public Health, Belgian "Fonds National de la Recherche Scientifique" (FNRS), "Centre Hospitalier" of the University of Liège, French Speaking Community of Belgium Concerted Research Action, the J.S. McDonnell Foundation, the European Commission, Mind Science Foundation, TX. SL, SM, and MB are, respectively, Senior Research Associate, Research Associate and Research Fellow at the FNRS. CS is funded by the "Fonds Léon Fredericq" (University of Liège) and the FNRS.

References

1. The Multi-Society Task Force on PVS: **Medical aspects of the persistent vegetative state (1).** *N Engl J Med* 1994, **330(21):**1499-1508.
2. Giacino J, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, *et al.*: **The minimally conscious state: Definition and diagnostic criteria.** *Neurology* 2002, **58(3):**349-353.
3. Majerus S, Gill-Thwaites H, Andrews K, Laureys S: **Behavioral evaluation of consciousness in severe brain damage.** *Prog Brain Res* 2005, **150:**397-413.
4. Gill-Thwaites H: **Lotteries, loopholes and luck: misdiagnosis in the vegetative state patient.** *Brain Inj* 2006, **20(13–14):**1321-1328.

5. Childs NL, Mercer WN, Childs HW: **Accuracy of diagnosis of persistent vegetative state.** *Neurology* 1993, **43(8):**1465-1467.
6. Andrews K, Murphy L, Munday R, Littlewood C: **Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit.** *BMJ* 1996, **313(7048):**13-16.
7. Andrews K: **Medical decision making in the vegetative state: withdrawal of nutrition and hydration.** *Neuro Rehabilitation* 2004, **19(4):**299-304.
8. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, Degueldre C, Aerts J, Luxen A, Franck G, *et al.*: **Cortical processing of noxious somatosensory stimuli in the persistent vegetative state.** *Neuroimage* 2002, **17(2):**732-741.
9. Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, Lancellotti P, Luxen A, Lamy M, Moonen G, *et al.*: **Perception of pain in the minimally conscious state with PET activation: an observational study.** *Lancet Neurol* 2008, **7:**1013-1020.
10. Giacino JT: **The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis.** *Neuro Rehabilitation* 2004, **19(4):**293-298.
11. Jennett B: **30 years of the vegetative state: clinical, ethical and legal problems.** In *The boundaries of consciousness: neurobiology and neuropathology Volume 150*. Edited by: Laureys S. Amsterdam: Elsevier; 2005:541-548.
12. Giacino J, Kalmar K, Whyte J: **The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility.** *Arch Phys Med Rehabil* 2004, **85(12):**2020-2029.
13. Teasdale G, Jennett B: **Assessment of coma and impaired consciousness. A practical scale.** *Lancet* 1974, **2(7872):**81-84.
14. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL: **Validation of a new coma scale: The FOUR score.** *Ann Neurol* 2005, **58(4):**585-593.
15. Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL: **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):**408-416.
16. Schnakers C, Giacino J, Kalmar K, Piret S, Lopez E, Boly M, Malone R, Laureys S: **Does the FOUR score correctly diagnose the vegetative and minimally conscious states?** *Ann Neurol* 2006, **60(6):**744-745. author reply 745
17. Schnakers C, Majerus S, Giacino J, Vanhaudenhuyse A, Bruno M, Boly M, Moonen G, Damas P, Lambermont B, Lamy M, *et al.*: **A French validation study of the Coma Recovery Scale-Revised (CRS-R).** *Brain Injury* 2008, **22(10):**786-792.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2377/9/35/prepub

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."
Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

BioMedcentral

ELSEVIER MASSON

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Revue générale

La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience

The Sensory Modality Assessment and Rehabilitation Technique (SMART): A behavioral assessment scale for disorders of consciousness

Q1 *C. Chatelle* [a,1], *C. Schnakers* [a,1], *M.-A. Bruno* [a,1], *O. Gosseries* [a,1], *S. Laureys* [a,b,1], *A. Vanhaudenhuyse* [a,*,1]

[a] *Coma Science Group, Cyclotron Research Center, University of Liège, Sart Tilman, B30, 4000 Liège, Belgique*
[b] *Département de neurologie, CHU Sart Tilman, Liège, Belgique*

INFO ARTICLE

Historique de l'article :
Reçu le 23 novembre 2009
Reçu sous la forme révisée le 25 décembre 2009
Accepté le 29 janvier 2010

Mots clés :
SMART
Évaluation comportementale
Traitement
État végétatif
État de conscience minimale

RÉSUMÉ

Introduction. – Le nombre persistant d'erreurs diagnostiques d'état végétatif (40 %) souligne l'importance d'utiliser des échelles d'évaluation sensibles pour détecter des signes de conscience chez ces patients non communicants.

État des connaissances. – La Sensory Modality Assessment and Rehabilitation Technique (SMART), échelle comportementale utilisant des stimulations sensorielles multimodales, semble être adaptée pour ce type d'évaluation. Plusieurs études ont montré sa sensibilité dans la discrimination de la conscience par rapport à d'autres échelles.

Perspectives. – Cet article présente une description de la procédure SMART, ainsi qu'une revue des études sur sa validité, sa fiabilité et sa robustesse. Une comparaison des réponses évaluées dans la SMART avec celles mesurées dans d'autres échelles standardisées validées est également proposée.

Conclusions. – Malgré certaines limites, la SMART semble adéquate pour un suivi à long terme des patients en état de conscience altérée mais son utilité en revalidation nécessite l'investigation de l'effet des stimulations sur l'évolution des patients. Étudier sa validité concourante avec d'autres échelles validées semble aussi nécessaire.

© 2010 Publié par Elsevier Masson SAS.

UNCORRECTED PROOF

---

[*] *Auteur correspondant.*

Q1 *E-mail address :* steven.laureys@ulg.ac.be (S. LQ1aureys), avanhaudenhuyse@doct.ulg.ac.be, avanhaudenhuyse@student.ulg.ac.be (A. Vanhaudenhuyse).

[1] http://www.comascience.org.

0035-3787/$ – see front matter © 2010 Publié par Elsevier Masson SAS.
doi:10.1016/j.neurol.2010.01.011

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Keywords:
SMART
Behavioral assessment
Treatment
Vegetative state
Minimally conscious state

ABSTRACT

Introduction. – Difficulties in detecting bedside signs of consciousness in non-communicative patients still lead to a high rate of misdiagnosis (CRSR) illustrating the need to employ standardized behavioral assessment scales.

State of art. – The Sensory Modality Assessment and Rehabilitation Technique (SMART) is a behavioral assessment scale of consciousness that assesses responses to multimodal sensory stimulation in disorders of consciousness. These stimulations can also be considered to have therapeutic value.

Perspectives. – We here review the different components and use of the SMART assessment and discuss its validity, reliability, and robustness in clinical practice. The scale has a high intra- and inter-observer reliability thanks to a detailed procedure description. However, in the absence of objective gold standards in the assessment of consciousness, it is currently difficult to make strong claims about its validity. A comparison between SMART and other standardized and validated coma-scales is proposed.

Conclusion. – In our view, SMART is an interesting tool for monitoring patients with altered states of consciousness subsequent to coma. Currently, we await studies on its concurrent validity as compared to other validated behavioral assessment scales and on the effect of SMART stimulations on patient outcome.

© 2010 Published by Elsevier Masson SAS.

UNCORRECTED PROOF

1. Introduction

Les progrès en médecine concernant la réanimation et les soins ont engendré une augmentation du nombre de patients survivant à de graves lésions cérébrales. Certains se rétablissent rapidement, tandis que d'autres traversent différents états tels que le coma, l'état végétatif et l'état de conscience minimale (pour une revue : Laureys et al., 2004). L'état végétatif est défini comme la récupération du cycle veille–sommeil en l'absence d'une réponse consciente, seules des réponses réflexes pouvant être observées (The Multi-Society Task Force on PVS, 1994). L'état de conscience minimale se caractérise par des comportements conscients et volontaires, bien que ceux-ci soient inconsistants et élémentaires, tels qu'une réponse à une commande simple, une poursuite visuelle et/ou une localisation de stimulations nociceptives ; sans communication fonctionnelle possible (Giacino et al., 2002). L'émergence de l'état de conscience minimale est caractérisée par la capacité du patient à communiquer ou à utiliser des objets de manière fonctionnelle (Giacino et al., 2002). Distinguer un patient en état végétatif d'un patient en état de conscience minimale demeure un véritable défi. En effet, 30 à 40 % des patients sont encore diagnostiqués étant en état végétatif alors qu'ils sont en réalité conscients (Schnakers et al., 2009) et ce, malgré l'introduction de nouveaux critères diagnostiques (Giacino et al., 2002). Ces résultats reflètent le manque de sensibilité des outils utilisés dans l'évaluation comportementale de la conscience. Actuellement, la Coma Recovery Scale-Revised (CRS-R – Giacino et al., 2004) a montré sa sensibilité par rapport aux autres échelles, celle-ci permettant de diminuer significativement l'erreur diagnostique (Schnakers et al., 2006, 2008). Elle semble selon nous être actuellement la référence standard pour l'évaluation comportementale de la conscience. Dans cet article, nous présenterons la Sensory Modality Assessment and Rehabilitation Technique (SMART – Gill-Thwaites, 1997 ; Gill-Thwaites et Munday, 1999), une échelle qui utilise des stimulations variées et multimodales et qui a montré son utilité dans la prise en charge clinique des patients en état de conscience altérée (Gill-Thwaites et Munday, 2004 ; Wilson et Gill-Thwaites, 2000). Nous comparerons cette échelle avec la CRS-R et d'autres échelles couramment utilisées en clinique telles que la Full Outline of Unresponsiveness (FOUR – Wijdicks et al., 2005), la Wessex Head Injury Matrix (WHIM – Shiel et al., 2000), la Glasgow Liège Scale (GLS – Born, 1988) et la Western Neuro Sensory Stimulation Profile (WNSSP – Ansell et Keenan, 1989).

2. SMART : une échelle d'évaluation et de traitement

La SMART a été créée par l'équipe de thérapie occupationnelle du Royal Hospital for Neuro-disability en 1988 et se base sur les paramètres de la Glasgow Coma Scale (Teasdale et Jennett, 1974). La procédure SMART est composée de deux types d'évaluation : l'une est informelle et l'autre formelle (Tableau 1). L'évaluation informelle comporte deux questionnaires remplis à la fois par la famille, les proches et par l'équipe soignante. Le premier questionnaire traite des habitudes de vie (goûts alimentaires, choix musicaux, etc.) du patient durant la période précédant son accident. Ces informations seront utiles pour l'évaluation, orienteront le traitement proposé. Il y est demandé d'indiquer ce que le patient aimait ou n'aimait pas avant son accident (musique, nourriture, etc.) afin d'évaluer l'intérêt des stimulations intégrées dans le protocole SMART. Le second questionnaire, proposé à toutes personnes étant en contact avec le patient, résume l'ensemble des comportements et réactions motrices observés chez le patient au cours de l'hospitalisation. Une feuille détaillée permet de définir la date, l'heure, la stimulation ayant provoqué la réponse observée, sa fréquence et sa durée.

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Tableau 1 – Protocole d'évaluation et de traitement SMART (adapté de Gill-Thwaites et Munday, 1999).
SMART Assessment and Treatment Protocol (adapted from Gill-Thwaites et Munday, 1999).

Étapes programme SMART	Durée et fréquence	Procédure	Responsabilités
1 : avant évaluation	À l'admission du patient ou précédant l'évaluation	Questionnaire sur les habitudes du patient avant l'accident Observation des comportements	Famille et personnel soignant
2 : évaluation SMART	Durant 3 semaines 10 sessions d'évaluation réparties en « matin » et « après-midi »	Observation des comportements spontanées × 10 SMART × 10	Examinateur
3 : bilan	Après 10 sessions d'évaluation	Mise en place du traitement sur la base des observations	Examinateur
4 : programme de traitement SMART	8 semaines (journalier) ou jusqu'à obtention du niveau 5 dans une des modalités (à 5 moments consécutifs), excepté l'éveil	Traitement SMART et observations des comportements	Examinateur Famille et personnel soignant
5 : révision du traitement	À l'obtention du niveau 5 dans une modalité ou tous les 2 mois durant 6 mois, puis tous les 6 mois	Processus d'évaluation SMART et révision du traitement selon les observations	Examinateur Famille et personnel soignant
6 : développement d'un système de communication	Durée et moment définis par l'équipe selon l'évolution observée	Mise en place d'un système de communication fonctionnelle	Examinateur Famille et personnel soignant

Les différents comportements sont ainsi notés systématiquement et permettent d'optimaliser la seconde partie de l'évaluation (l'administration formelle de la SMART). L'évaluation formelle (de la SMART) est réalisée par un clinicien entraîné et consiste à évaluer les réponses comportementales à différentes stimulations. Après avoir observé les comportements spontanés du patient durant dix minutes (ligne de base), les réactions observées suite aux différentes stimulations administrées seront notées et rapportées par le clinicien. En plus d'être une échelle d'évaluation, l'intérêt principal de la SMART est qu'elle peut être administrée en tant qu'outil thérapeutique de stimulation sensorielle. Cependant, aucune étude n'a pu mettre en évidence l'effet à long terme de ces stimulations sur l'évolution de patients en état de conscience altérée.

L'évaluation formelle permet de situer l'état du patient et d'obtenir des informations sur ses capacités motrices, communicationnelles et sensorielles. Les observations faites durant ces évaluations influenceront la phase de traitement. Le patient est évalué sur dix sessions journalières pendant trois semaines ; cinq évaluations se font le matin et cinq l'après-midi, cela afin de déterminer la période durant laquelle le patient est le plus répondant. Après les dix évaluations, le traitement sera mis en place sur la base des observations des cliniciens.

L'examinateur décidera de stimuler une modalité en particulier si le patient se montre particulièrement réactif à ce type de stimulation durant la période d'évaluation. Par ailleurs, les stimulations peuvent intégrer du matériel plus personnel, comme par exemple des photographies de proches, des odeurs particulières, etc. Cette phase de traitement a lieu au minimum une fois par jour pendant au moins deux mois. Elle dure environ 30 minutes et toutes les réponses sont notées.

Avant de commencer l'administration de la SMART, l'examinateur se présente au patient et donne des informations spatiotemporelles. Celles-ci seront répétées à la fin de la session. Dix minutes d'observation sans stimulation sont nécessaires avant de débuter l'évaluation (ligne de base). La SMART évalue huit modalités : cinq modalités sensorielles (visuelle, tactile, auditive, olfactive et gustative), la motricité, la communication fonctionnelle ainsi que la vigilance. Pour chaque modalité, le protocole décrit explicitement les instructions à donner aux patients, le matériel utilisé, la position de l'examinateur, les observations à faire, ainsi que quelques conseils à prendre en compte durant l'évaluation (exemple : en cas de cécité, paralysie).

Les conditions engendrant un arrêt ou la non-administration d'une partie de l'échelle sont précisées (patient atteint de cécité, de surdité, paralysie, allergies, trachéotomie, etc.). Au cours de l'évaluation, si le patient répond aux indications écrites et non aux indications orales, l'examinateur devra utiliser la modalité visuelle. Chaque stimulation est précédée de dix secondes et suivie de 20 secondes d'observation et ce, afin de distinguer les comportements réflexes des comportements volontaires. Un total de dix évaluations est nécessaire avant d'effectuer un avis quant au diagnostic. Les auteurs suggèrent de varier l'ordre de présentation des différentes modalités. Un code précis est utilisé afin de coter les réponses observées ; pas de réponse se code par [-], réponse inexacte par [In], réponse exacte par [x], réponse retardée par [NR] et ambiguë par [?]. Le côté où apparaît la réponse doit aussi être noté (gauche ou droit). Le Tableau 2 reprend les différents comportements observés selon les modalités.

Étant une échelle graduelle, le niveau de cotation augmente avec la complexité des réponses observées. Cinq niveaux sont décrits :

- niveau 1 : pas de réponse : aucune réponse ne peut être observée ;
- niveau 2 : réponses réflexes : réponses stéréotypées et réflexes (flexion, extension ou sursaut) ;

UNCORRECTED

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Tableau 2 – Résumé des différents comportements observés pour chaque modalité de la SMART.
Summary of the observed behaviors in SMART modalities.

Modalités	Types de réponses	Réponses observées	Cotation
Modalité visuelle	Réflexe	1. Réflexe pupillaire à la lumière 2. Clignement des paupières à la lumière 3. Réponse visuelle à la menace (mouvements rapides devant chaque œil)	Niveau 1 : absence de réponse Niveau 2 : réflexe présence de (1) ou (2) Niveau 3 : présence de (3) Niveau 4 : présence de (5), (6) ou (7) Niveau 5 : (8), (9) ou (10) réalisés
	Retrait (réflexe)	4. Évitement de la stimulation	
	Localisation	5 et 6. Fixation et poursuite visuelles avec des objets et photographies 7. Poursuite visuelle de l'examinateur	
	Discrimination	8. Réalisation d'indications écrites (3 à 6 indications présentées) 9. Capacité à utiliser un contacteur sur indications écrites (s'il sait le faire, utilisation du contacteur pour des réponses oui/non dans la partie « communication ») 10. Discrimination de stimuli visuels (couleurs et oui/non)	
Modalité auditive	Réflexe	1. Clignements, sursaut, expressions faciales, flexion, extension, ouverture des yeux	Niveau 1 : absence de réponse Niveau 2 : présence de comportements inclus dans (1) Niveau 3 : (2) ou (3) présents Niveau 4 : présence de (4) Niveau 5 : réalisation de (5) ou (6)
	Retrait (réflexe)	2. Habituation aux sons 3. Évitement de la stimulation	
	Localisation	4. Localise la stimulation	
	Discrimination	5. Réalisation d'indications orales (3 à 6 indications présentées) 6. Capacité à utiliser un contacteur sur indication orale	
Modalité tactile	Réflexe	1. Flexion, extension, réflexes oraux, clignements des yeux, expressions faciales, augmentation de l'inhalation, ouverture des yeux, sursaut	Niveau 1 : absence de réponse Niveau 2 : présence des comportements inclus dans (1) Niveau 3 : présence de (2) Niveau 4 : présence de (3) Niveau 5 : (5) réalisé
	Retrait (réflexe)	2. Évite la stimulation	
	Localisation	3. Localise la stimulation 4. Expression faciale de type communicative	
	Discrimination	5. Capacité de différencier stimuli tactiles contrastés (chaud/froid)	
Modalité olfactive	Réflexe	1. Flexion, extension, réflexes oraux, clignement des yeux, expressions faciales, augmentation de l'inhalation, ouverture des yeux, sursaut	Niveau 1 : absence de réponse Niveau 2 : présence des comportements inclus dans (1) Niveau 3 : présence de (2) ou (3) Niveau 4 : présence de (4) ou (5) Niveau 5 : (6) réalisé
	Retrait (réflexe)	2. Évite la stimulation 3. Diminution de l'inhalation	
	Localisation	4. Localise la stimulation 5. Augmentation de l'inhalation accompagnée d'une expression faciale plaisante de type communicatif	
	Discrimination	6. Discrimination de stimuli olfactifs contrastés (ail/café)	
Modalité gustative	Réflexe	1. Flexion, extension, réflexes oraux, clignement des yeux, expressions faciales, ouverture des yeux, sursaut	Niveau 1 : absence de réponse Niveau 2 : présence des comportements inclus dans (1) Niveau 3 : présence de (2) et (3) Niveau 4 : présence de (4) ou (5) Niveau 5 : réalisation de (6)
	Retrait (réflexe)	2. Évite la stimulation 3. Fermeture de la bouche	
	Localisation	4. Ouverture de la bouche ou relâchement de la mâchoire 5. Expression faciale communicative	
	Discrimination	6. Discrimination de stimuli gustatifs contrastés (sel/citron)	

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Tableau 2 *(Continued)*

Modalités	Types de réponses	Réponses observées	Cotation
Modalité motrice	Réflexe	1. Flexion, extension, *grasping*, clignement des yeux	Niveau 1 : absence de réponse Niveau 2 : présence des comportements inclus dans (1) Niveau 3 : présence de (2), (3) ou (4) Niveau 4 : présence de (5), (6), (7) ou (8) Niveau 5 atteint lorsque les items (9) ou (10) sont réalisés
	Mouvement non contextualisé/retrait	2. Mouvements présents en l'absence de stimulation 3. Utilisation non fonctionnelle d'objets 4. Évite la stimulation	
	Mouvement contextualisé/localisation (< 5 observations)	5. Réponses aux commandes visuelles/orales 6. Utilisation fonctionnelle inconsistante d'objets 7. Mouvement de résistance ou de rejet de la stimulation 8. Localise la stimulation	
	Mouvement contextualisé (> 5 observations)	9. Réponses consistantes aux commandes visuelles/orales 10. Utilisation fonctionnelle et consistante d'objets	
Communication	Non spécifique	1. Vocalisations, expressions faciales, rires non spécifiques à la stimulation	Niveau 1 : absence de réponse Niveau 2 : présence des comportements inclus dans (1) Niveau 3 : présence de (2) Niveau 4 : présence de (3) ou (4) Niveau 5 : réalisation de (5), (6) ou (7)
	Spécifique	2. Vocalisations, expressions faciales, rires, gestes spécifiques à la stimulation	
	Communication inconsistante (< 5 observations)	3. Gestes, expressions faciales, verbalisations inconsistants avec les stimulations 4. Réponses oui/non inconsistantes dans les différentes modalités	
	Communication consistante (> 5 observations)	5. Gestes, expressions faciales, verbalisations consistants avec les stimulations 6. Réponses oui/non consistantes dans les différentes modalités 7. Expression par écrit ou via un *buzzer*	
Modalité vigilance	Aucun éveil	1. Yeux clos durant toute l'évaluation	Niveau 1 : présence de (1) Niveau 2 : nécessité de (2) Niveau 3 : nécessité de (3) Niveau 4 : présence de (4) Niveau 5 : présence de (5)
	Éveil minimal	2. Plus de 5 stimulations nécessaires pour maintenir l'éveil	
	Éveil moyen	3. 2–4 stimulations nécessaires pour maintenir l'éveil	
	Éveil normal	4. 1 stimulation nécessaire pour maintenir l'éveil	
	Éveil optimal	5. Éveil constant	

- niveau 3 : retrait : mouvements de retrait ;
- niveau 4 : localisation : réponses orientées ;
- niveau 5 : réponses différenciées : réponses adéquates à une commande visuelle ou verbale ; utilisation fonctionnelle d'objet.

La SMART ne permet pas d'émettre un diagnostic uniquement sur la base des niveaux de réponses du patient. En effet, les réponses de niveau 1, 2 ou 3 peuvent être observées chez les patients en coma ou en état végétatif. Les réponses de niveau 4 peuvent être présentes chez un patient en état végétatif et en état de conscience minimale, alors qu'un patient en état de conscience minimale ou émergeant de cet état présente des comportements de niveau 5 (Tableau 3).

Le score total ne se compose pas de l'ensemble des scores dans les différentes modalités ; chaque modalité est considérée individuellement comme un score unique. Lorsqu'une réponse du niveau 5 (voir paragraphe suivant) apparaît comme constante au cours de cinq évaluations consécutives dans une modalité (excepté la vigilance), on peut conclure à une récupération de la conscience. Le traitement peut être modifié ou arrêté si les réponses aux stimulations sont constantes et significatives. À l'inverse, l'absence d'une réponse constante de niveau 5 mènera à une prolongation de deux mois avec révision tous les deux mois durant six mois, ensuite le programme sera revu tous les six mois. Selon l'évolution du patient, les cliniciens vont ensuite mettre en place un système de communication, cela en collaboration avec les proches et le personnel soignant.

3. Sensibilité et fiabilité de la SMART

Lors d'une étude réalisée auprès de 30 patients en état végétatif comparant la WNSSP, la SMART ainsi que la Rancho Levels of Cognitive Functioning (Rancho – Gill-Thwaites, 1997 ;

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Tableau 3 – Niveaux définis par la SMART, diagnostic et traits cliniques associés.
SMART levels, diagnosis and clinical features.

Niveaux	Diagnostic	Traits cliniques
1	Coma	Yeux fermés. Pas de réponse
1	EV	Yeux ouverts. Pas de réponse
2–3	Coma	Yeux fermés. Mouvements réflexes à la stimulation nociceptive. Pas d'autre réponse
2–3	EV	Yeux ouverts. Réponses réflexes et de retrait
4	EV/ECM	Comportement montrant un ECM. Nécessite l'établissement de la qualité et consistance des réponses pour définir si EV ou ECM
5	ECM/émergence de l'ECM	Réponse consistante indiquant un niveau de conscience. Sortie de l'EV. Nécessite d'autres évaluations pour établir les possibilités futures

EV : état végétatif ; ECM : état de conscience minimale.

Malkmus et al., 1980), les auteurs ont mis en évidence que la SMART et la Rancho différaient significativement quant au diagnostic. Les résultats démontraient que la SMART détectait un fonctionnement cognitif plus élevé chez les patients. De plus, sur six patients détectés avec la SMART comme émergeant de l'état végétatif au cours de l'étude, seulement deux l'ont été avec la WNSSP. Ces résultats peuvent s'expliquer par le fait que, contrairement à la WNSSP, la SMART comporte différentes modalités, chacune examinée indépendamment des autres. Chaque score a donc une valeur indépendante et l'évaluation globale ne consiste pas en une addition des scores mais en l'interprétation de ceux-ci pour chaque modalité.

Par ailleurs, Wilson et Gill-Thwaites (2000) ont démontré l'intérêt des scores totaux de la SMART dans le pronostic des patients en état végétatif. Une différence significative a été observée dans les scores obtenus chez les patients végétatifs selon qu'ils avaient récupéré au cours de l'étude ou non. Ce constat n'était pas généralisable à la WNSSP. Les auteurs expliquaient cela par le fait que la WNSSP considère toutes les réponses moins complexes que la localisation (niveau 4 dans la SMART) comme une absence de réponse. Ajoutons que l'importance du score pour chaque modalité est également répartie dans la SMART, alors que dans la WNSSP, la modalité visuelle a plus d'importance dans le score total. Andrews et al. (1996) ont démontré que 65 % des patients ayant été mal diagnostiqués étaient aveugles ou fortement atteints visuellement.

Enfin, une bonne fiabilité intra- et interjuges a été rapportée pour la SMART, la précision de ses items limitant les variations trop importantes dans la cotation (Gill-Thwaites et Munday, 2004). Dans cette étude, deux examinateurs ont évalué 60 patients diagnostiqués en état végétatif à l'admission, et cela dans la première semaine et tous les deux mois à partir de leur hospitalisation. La corrélation intrajuge obtenue était de 0,97, et la corrélation interjuge, de 0,96. Ces résultats démontrent une faible variabilité dans les scores obtenus entre évaluateurs et sur plusieurs évaluations effectuées par un même évaluateur. La validité est en revanche difficile à apprécier, étant donné qu'il n'y a pas de consensus concernant une échelle de référence commune. Cependant, étant donné que la CRS-R a montré une plus grande sensibilité par rapport au diagnostic, il semblerait utile de comparer la SMART à cette dernière.

4. Comparaison entre la SMART et d'autres échelles standardisées et validées

Tout comme la CRS-R, la FOUR, la WHIM, la GLS et la WNSSP, la SMART évalue la poursuite visuelle qui est considérée comme un des premiers signes de conscience réapparaissant chez les patients sévèrement cérébrolésés (Giacino et al., 2002) (Tableau 4). La fixation est également reprise dans chacune de ces échelles sauf dans la FOUR et la WNSSP. Cependant, la SMART permet à l'examinateur d'utiliser diverses stimulations pour évaluer la poursuite visuelle des patients, alors que la CRS-R insiste sur l'utilisation d'un miroir, outil ayant été démontré comme significativement plus sensible pour détecter ce comportement (Vanhaudenhuyse et al., 2008). Dans la modalité auditive, la SMART est la seule échelle à évaluer les comportements d'habituation et de retrait par rapport à une source sonore. Néanmoins, aucune étude jusqu'à ce jour n'a démontré l'utilité de ces items pour le diagnostic des patients en état de conscience altérée. Notons que la SMART et la WNSSP évaluent toutes deux les réponses du patient à une stimulation tactile non douloureuse, mais elles ne s'intéressent pas aux réponses à la stimulation tactile douloureuse. Ce type de stimulus est utilisé dans la CRS-R, la FOUR et la GLS. Aucune donnée ne permet de valider l'utilisation d'une stimulation douloureuse dans l'évaluation de la conscience. Nous pouvons également remarquer que la SMART et la WNSSP évaluent les réponses à des stimulations olfactives, la SMART utilise aussi les stimulations gustatives alors que les autres n'en tiennent pas compte. L'intérêt de ces modalités dans l'évaluation de la conscience chez des patients sévèrement cérébrolésés n'a cependant pas encore été démontré. Enfin, la CRS-R est la seule échelle à évaluer tous les réflexes du tronc cérébral (réflexes fronto-orbiculaire, pupillaire, cornéen, oculocéphaliques verticaux/horizontaux, oculocardiaque et nauséeux ; les mouvements spontanés des yeux et les réponses stéréotypées). La SMART, quant à elle, ne s'intéresse qu'aux réflexes pupillaires et aux réponses stéréotypées. Cette évaluation a toute son importance chez les patients en état de conscience altérée car elle permet de détecter s'il y a des lésions structurelles au niveau du circuit de l'éveil, les fonctions du tronc ainsi que les circuits moteurs étant adjacents à ce système. Les réponses oculomotrices sont particulièrement informatives quant à la préservation du système d'éveil (Posner et al., 2007).

UNCORRECTED PROOF

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Tableau 4 – Tableau comparatif des comportements observés dans la SMART (Gill-Thwaites et Munday, 1999), la Coma Recovery Scale-Revised (CRS-R, Giacino et al., 2004), la Full Outline of Unresponsiveness (FOUR, Wijdicks et al., 2005), la Wessex Head Injury Matrix (WHIM, Shiel et al., 2000), la Glasgow Liège Scale (GLS, Born, 1988) et la Western Neuro Sensory Stimulation Profile (WNSSP, Ansell et Keenan, 1989).
Comparison table between SMART, CRS-R, FOUR, WHIM, GLS and WNSSP for behavioral responses assessed.

	Réponses comportementales	SMART	CRS-R	FOUR	WHIM	GLS	WNSSP
Vigilance		X	X	X	X	X	X
Visuel	Ouverture des yeux/éveil	X	X	X	X	X	X
	Réflexe de clignement à la menace	X	X				
	Fixation	X	X		X		
	Poursuite visuelle	X	X	X	X		X
	Discrimination visuelle	X	X		X		
	Compréhension de commande visuelle	X					X
Auditif	Réflexe de sursaut au bruit	X	X	X		X	X
	Habituation au bruit	X					
	Mouvement de retrait	X					
	Localisation de son	X	X		X		X
	Compréhension de commande	X	X	X	X	X	X
Verbal/Communication	Réflexes oraux	X	X		X		
	Vocalisation/mouvements oraux	X	X		X	X	X
	Verbalisation intelligible	X	X		X	X	X
	Communication non fonctionnelle intentionnelle	X	X		X	X	X
	Communication fonctionnelle intentionnelle	X	X		X	X	
	Orientation				X	X	
Tactile (non douloureux)	Réponses stéréotypées	X					X
	Flexion	X					X
	Localisation	X					X
	Discrimination	X					
Tactile nociceptif	Réponses stéréotypées		X	X		X	
	Flexion		X	X		X	
	Localisation		X	X		X	
Olfactif	Réponses réflexes	X					X
	Mouvement de retrait	X					
	Localisation	X					
	Discrimination	X					X
Gustatif	Réponses réflexes	X					
	Mouvement de retrait	X					
	Localisation	X					
	Discrimination	X					
Respiration				X			
Réflexes du tronc cérébral	Fronto-orbiculaire		X			X	
	Pupillaire	X	X	X		X	
	Cornéen		X	X			
	Mouvements spontanés des yeux		X				
	Oculocéphalique vertical		X			X	
	Oculocéphalique horizontal		X			X	
	Réponses stéréotypées	X	X	X		X	
	Oculocardiaque					X	
	Nauséeux		X	X			

Un danger de la SMART est qu'une seule réponse est suffisante pour atteindre un niveau, et bien que cela offre une information sur la meilleure réponse du sujet, cette dernière peut aussi être due au hasard (exemple : contraction involontaire de la main du patient apparaissant lorsque l'examinateur lui demande de lui serrer la main). La SMART a en revanche comme atout le nombre important de stimulations et modalités utilisées et la prise en compte des informations provenant des proches. Cela permet l'utilisation de stimulations, personnalisées ou non, comme traitement, ce qui n'est pas envisageable avec les autres échelles, bien qu'il n'y ait pas encore eu à ce jour d'étude sur les effets réels de ces stimulations dans l'évolution de la conscience de ces patients.

5. Comment devenir un examinateur SMART ?

Une formation SMART est proposée par l'institut de réadaptation neuropalliative à Londres. Elle est payante et obligatoire

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

pour toutes personnes désirant utiliser cette échelle. Un certain nombre de qualités d'observation et de compétences cliniques est requis pour la réussite de cette formation. La participation aux cours ainsi qu'un travail pratique permettront aux participants de devenir des examinateurs SMART. Une compréhension de l'anglais est indispensable pour participer à la formation, dans le cas contraire, une alternative doit être envisagée avec les formateurs. La formation dure cinq jours. Une première journée introduit l'évaluation et le traitement chez les patients en état végétatif et en état de conscience minimale. Les quatre autres journées de cours permettront un apprentissage approfondi du protocole de la SMART comme évaluation et comme traitement.

6. Conclusion

Des études ont montré que la SMART était plus sensible que la WNSSP et la Rancho dans l'évaluation des patients. Cependant, aucune étude n'a actuellement été réalisée comparant la SMART à la CRS-R, échelle qui a pourtant montré sa sensibilité par rapport à d'autres échelles telles que la WHIM et la FOUR dans la détection de signe de conscience. La SMART semble, par ailleurs, utile dans le suivi des patients à long terme et en revalidation. Elle permet d'évaluer les réponses du patient à un nombre élevé de stimulations sensorielles, et cela dans différentes modalités, toutes cotées indépendamment les unes des autres. Ces mêmes stimulations peuvent aussi être utilisées par la suite dans une phase de traitement. Le protocole de la SMART est précis et détaillé quant au déroulement de l'évaluation, ce qui lui procure une bonne fiabilité intra- et interjuges. Un autre 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 d'une grande importance pour l'évaluation et peuvent influer sur le choix des stimulations administrées au patient lors de la phase de traitement.

Par ailleurs, en tant qu'échelle comportementale, la SMART fait preuve de certaines limites. En effet, son utilisation clinique est difficile, non seulement par le temps d'administration de l'échelle qui s'élève à environ 45 minutes, mais aussi car le nombre d'évaluations et le temps nécessaire à l'obtention d'un diagnostic sont longs. Elle n'est donc, par exemple, pas adaptée au contexte d'évaluation en unités de soins intensifs. De plus, les critères diagnostiques définis selon les cinq niveaux sont vastes et ne permettent pas un diagnostic précis. De futures études comparatives sont nécessaires afin d'étudier sa validité concourante avec des échelles standardisées utilisées en clinique telles que la FOUR, la WHIM et la GLS. Il semble particulièrement intéressant de la confronter à la CRS-R, qui selon nous est actuellement l'échelle de référence. En effet, certaines différences dans le choix des items dans ces échelles impliquent une vérification de leur utilité dans l'observation diagnostique. De plus, une évaluation de l'effet de l'échelle en tant que traitement devra aussi être faite afin de connaître son utilité en réhabilitation.

Conflit d'intérêt

Aucun.

Remerciements

Ce travail a bénéficié du soutien du Fonds de la recherche scientifique (FRS), de la Commission européenne (DISCOS, Mindbridge, DECODER & CATIA), de l'Action de recherche concertée (ARC-06/11-340), la McDonnell Foundation et de la Mind Science Foundation.

RÉFÉRENCES

Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. Br Med J 1996;313:13–6.

Ansell BJ, Keenan JE. The Western Neuro Sensory Stimulation Profile: a tool for assessing slow-to-recover head-injured patients. Arch Phys Med Rehabil 1989;70:104–8.

Born JD. The Glasgow Liège Scale: prognostic value and evolution of motor responses and brain stem reflexes after head injury. Acta Neurochir (Wien) 1988;91:1–11.

Giacino J, Ashwal S, Childs N, Cranford R, Jennett B, Katz D, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349–53.

Giacino J, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020–9.

Gill-Thwaites H. The Sensory Modality Assessment Rehabilitation Technique – a tool for assessment and treatment of patients with severe brain injury in a vegetative state. Brain Inj 1997;11:723–34.

Gill-Thwaites H, Munday R. The Sensory Modality Assessment and Rehabilitation Technique (SMART): a comprehensive and integrated assessment and treatment protocol for the vegetative state and minimally responsive patient. Neuropsychol Rehabil 1999;9:305–20.

Gill-Thwaites H, Munday R. The sensory modality assessment and rehabilitation technique (SMART): a valid and reliable assessment for vegetative state and minimally conscious state patients. Brain Inj 2004;18:1255–69.

Laureys S, Owen A, Schiff D. Brain function in coma, vegetative state and related disorders. Lancet 2004;3:537–46.

Malkmus D, Booth B, Kodimer C. Rehabiliation of the head injured adult: comprehensive cognitive management: Professional Staff Association of Rancho Los Amigos Hospital. California: Downey; 1980.

Posner J, Saper C, Schiff N, Plum F. Plum and Posner's diagnosis of stupor and coma. New York: Oxford University Press; 2007.

Schnakers C, Giacino J, Kalmar K, Piret S, Lopez E, Boly M, et al. Does the FOUR score correctly diagnose the vegetative and minimally conscious states? Ann Neurol 2006;60:744–5.

Schnakers C, Majerus S, Giacino J, Vanhaudenhuyse A, Bruno M, Boly M, et al. A French validation study of the Coma Recovery Scale-Revised (CRS-R). Brain Inj 2008;22:786–92.

Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9. Q2

UNCORRECTED PROOF

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL. 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;14:408–16.

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81–4.

The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med 1994;330:1499–508.

Vanhaudenhuyse A, Schnakers C, Brédart S, Laureys S. Assessment of visual pursuit in post-comatose sates: use a mirror. J Neurol Neurosurg Psychiatry 2008;79:223.

Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. Ann Neurol 2005;58:585–93.

Wilson S, Gill-Thwaites H. Early indication of emergence from vegetative state derived from assessments with the SMART – a preliminary report. Brain Inj 2000;14:319–31.

UNCORRECTED PROOF

Pour citer cet article : Chatelle C, et al., La Sensory Modality Assessment and Rehabilitation Technique (SMART) : une échelle comportementale d'évaluation et de revalidation pour des états altérés de conscience, Revue neurologique (2010), doi:10.1016/j.neurol.2010.01.011

LETTERS

Assessment of visual pursuit in post-comatose states: use a mirror

One of the first clinical signs differentiating the minimally conscious state (MCS) from the vegetative state is the presence of visual pursuit occurring in direct response to moving or salient stimuli.[1] At present, there is no consensus on what visual stimulus should be employed at the patient's bedside in the assessment of visual pursuit in post-comatose states. Indeed, several behavioural "coma scales" use different stimuli to evaluate visual pursuit: the Coma Recovery Scale-Revised (CRS-R) and Western Neuro-Sensory Stimulation Profile (WNSSP) employ a moving mirror; the Coma/Near Coma Scale, Wessex Head Injury Matrix (WHIM) and Sensory Modalities Assessment and Rehabilitation Technique (SMART) use a moving person; the WNSSP, SMART, WHIM and Full Outline of Unresponsiveness Scale use a moving object or finger (for references see review by Majerus and colleagues[2]).

The aim of the present study was to determine whether the assessment of pursuit eye movements in MCS is influenced by the choice of the visual stimulus. Therefore, we prospectively studied visual pursuit using a standardised presentation of a moving mirror compared with a moving person and a moving object.

METHODS

MCS patients were studied free of sedative drugs in the acute (ie, within 4 weeks) and chronic (ie, more than 4 weeks after insult) setting. The diagnosis of MCS was made according to the Aspen workgroup criteria for MCS[1] and based on CRS-R assessment made by two experienced and skilled neuropsychologists (AV and CS). Each patient was assessed in the sitting position and patient preparation employed a standardised arousal facilitation protocol, as defined in the CRS-R. The goal of this intervention was to prolong the length of time the patient maintained arousal.

Table 1 Number of minimally conscious patients showing visual pursuit (n = 38) as a function of the stimulus used

Stimulus	No of patients showing visual pursuit (%)
Mirror only	11 (29)
Person only	2 (5)
Object only	0 (0)
Mirror and person	4 (11)
Mirror and object	2 (5)
Person and object	0 (0)
Mirror, person and object	19 (50)

Visual pursuit was evaluated using a standardised methodology, as described in the CRS-R (mirror tracking) and the WHIM (person and object tracking). In brief, a round mirror (diameter 15.2 cm) or object (11.4 cm; ball or cup) was held 15.2 cm in front of the patient's face and was moved slowly 45° to the right and left of the vertical midline. For visual pursuit assessment using a moving person, the examiner walked slowly 45° to the right and left of the vertical midline. Stimuli were presented twice for each direction and the order of presentation was randomised. Visual pursuit was defined as a full range (ie, 45°) eye movement without loss of fixation on two occasions in any direction. If the above criterion was not met, the procedure was repeated assessing one eye at a time using an eye patch.

Differences between visual pursuit, as assessed by the mirror, person or object, were assessed using binomial testing. Results were considered significant at a p value <0.05.

RESULTS

Of 51 patients included (36 men; mean age 59 (SD 17) years), 28 (55%) were studied in the acute (mean interval 15 (6) days) and 23 (45%) in the chronic (4 (21) months) setting. Aetiology was traumatic in 24 (47%) and non-traumatic in 27 (53%) patients (ie, ischaemic or haemorrhagic stroke (n = 11), anoxic encephalopathy (n = 11), metabolic encephalopathy (n = 3) and toxic encephalopathy (n = 2)). Thirty-eight (75%) of the 51 MCS patients showed pursuit eye movement occurring in response to moving salient stimuli.

In the 38 MCS patients showing pursuit eye movements, 36 tracked a moving mirror (95%; 18 traumatic; 20 acute) compared with 25 who tracked a moving person (66%; $p<0.01$; 12 traumatic; 14 acute) and 21 who tracked a moving object (55%; $p<0.01$; nine traumatic; 15 acute) (table 1).

The difference between visual pursuit assessed by using a moving person or a moving object was not significant. Visual pursuit preference was not significantly different in terms of aetiology or time since insult.

DISCUSSION

Our data show that the clinical assessment of visual pursuit depends on what moving stimulus is used. MCS patients tend to best track their own reflection as compared with tracking a moving person or object. In everyday social interactions, autoreferential stimuli capture our attention and give rise to a sense of self-awareness, as reflected in the cocktail party phenomenon when hearing our own name. Similarly, we have shown that seeing one's own face also has very strong attention grabbing properties in healthy subjects.[3] Previous functional imaging studies have shown activation of anterior and posterior midline structures (ie, mesiofrontal and precuneal cortices) during self-face presentation in healthy volunteers (for review see Laureys and colleagues[4]). Interestingly, these areas are amid the most metabolically impaired in patients in a vegetative state, incapable of sustained visual pursuit.[5]

Thirteen of 51 patients failed to show visual pursuit (25%). Neurological assessment showed that five of these 13 patients (38%) failed to eye blink to threat; the remaining eight patients (62%) had intact brainstem reflexes while showing reproducible but inconsistent command following. In line with previous studies,[6] visual impairment probably explains this finding.

Two patients showed visual pursuit to a stimulus other that the mirror. In both cases, presentation of the mirror was used as the last stimulus and hence fatigue might explain exceptional tracking of a moving person in the absence of mirror tracking. MCS patients typically show fluctuating signs of voluntary interaction with their environment and observed responses may be easily exhausted (eg, see Giacino and colleagues[1]).

The clinical implications of our findings are important as more than a fifth of the MCS patients with visual pursuit only tracked a moving mirror (and not a moving person or object) and hence would have been misdiagnosed as being vegetative. Our findings emphasise the importance of using a mirror when evaluating eye tracking in post-comatose states.

A Vanhaudenhuyse,[1] C Schnakers,[1] S Brédart,[3] S Laureys[1,2]

[1] Coma Science Group and Cyclotron Research Centre, University of Liège, Belgium; [2] Department of Neurology, University of Liège, Belgium; [3] Department of Cognitive Science, University of Liège, Belgium

Correspondence to: Professor S Laureys, Coma Science Group, Cyclotron Research Centre, University of Liège, Sart Tilman B30, 4000 Liège, Belgium; steven.laureys@ulg.ac.be

Funding: This research was funded by the Belgian Fonds National de la Recherche Scientifique (FNRS), the French Speaking Community of Belgium Concerted Research Action 06/11-340 and the European Commission. SL is Senior Research Associate at FNRS.

Competing interests: None.

J Neurol Neurosurg Psychiatry 2008;**79**:223. doi:10.1136/jnnp.2007.121624

REFERENCES

1. **Giacino JT,** Ashwal S, Childs N, *et al*. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002;**58**:349–53.
2. **Majerus S,** Gill-Thwaites H, Andrews K, *et al*. Behavioral evaluation of consciousness in severe brain damage. *Prog Brain Res* 2005;**150**:397–413.
3. **Bredart S,** Delchambre M, Laureys S. One's own face is hard to ignore. *Q J Exp Psychol* 2006;**59**:46–52.
4. **Laureys S,** Perrin F, Bredart S. Self-consciousness in non-communicative patients. *Conscious Cogn* 2007;**16**:722–41.
5. **Laureys S,** Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 2004;**3**:537–46.
6. **Andrews K,** Murphy L, Munday R, *et al*. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ* 1996;**313**:13–16.

Clinical/Scientific Notes

A. Vanhaudenhuyse, MSc
J. Giacino, PhD
C. Schnakers, MSc, PhD
K. Kalmar, PhD
C. Smart, PhD
M.-A. Bruno, MSc
O. Gosseries, MSc
G. Moonen, MD, PhD
S. Laureys, MD, PhD

Supplemental data at www.neurology.org

BLINK TO VISUAL THREAT DOES NOT HERALD CONSCIOUSNESS IN THE VEGETATIVE STATE

The blink response to visual threat is a standard bedside method for testing visual processing. In response to a sudden gesture directed toward the eyes, a person with a normal blink response will promptly contract both orbicularis oculi muscles to close the eyelids momentarily. There is no consensus as to whether blinking to visual threat (BVT) is purely reflex[1] or a cognitively mediated behavior that heralds consciousness; i.e., is incompatible with the diagnosis of the vegetative state (VS).[2,3] Some authors stated that "one should be extremely cautious in making the diagnosis of the VS when there is . . . response to threatening gestures."[4] Others stated that "react(ion) to visual threat" is a "compatible but atypical feature" of VS.[5] Similarly, other guidelines stated that the "threat response is usually absent" in VS.[6] Finally, BVT was not mentioned in some workgroup criteria on the minimally conscious state.[7]

The aim of the study was to determine the incidence of BVT in patients whose clinical features are in all other respects typical of the VS, as assessed by means of validated testing.[7] We also investigated whether the presence of BVT in patients considered vegetative is predictive of recovery of consciousness.

Methods. The BVT was assessed (four trials per eye) in patients in a VS (by means of the Coma Recovery Scale Revised [CRS-R])[7] of traumatic or nontraumatic etiology in the acute (<4 weeks) or subacute setting (≥4 weeks), by quickly moving a finger 1 inch in front of the patient's eye, while avoiding contact with the eyelashes or inadvertent production of a breeze. All patients were assessed free of sedative drugs. As stated elsewhere,[7,3] BVT was defined as a blink promptly following presentation of visual threat on at least two trials with either eye. To avoid misinterpreting spontaneous blinks as BVT, we tested patients between spontaneous blinks. However, in the absence of a controlled laboratory protocol, this bias cannot be formally excluded. Outcome was studied at 1 year for traumatic and 3 months for nontraumatic cases. Patients who died or remained vegetative (unfavorable outcome) were compared to patients who recovered from VS (favorable outcome). Differences between outcomes in patients with and without blink were calculated using χ^2 testing, thresholded for significance at $p < 0.05$.

Results. Out of 91 patients with VS included (60 in New Jersey and 31 in Liège; mean age 45 ± 20 years), 19 were studied in the acute (15 ± 6 days post-insult), and 72 in the subacute setting (3 ± 5 months post-insult). Etiology was traumatic in 41 and nontraumatic in 50 patients (i.e., anoxic encephalopathy [n = 27], ischemic or hemorrhagic stroke [n = 12], metabolic encephalopathy [n = 8], and tumor [n = 3]). Forty-six out of the 91 patients (51%) showed BVT (32 subacute; 26 nontraumatic). In these 46 patients, 10 died (7 nontraumatic), 22 remained in VS (14 nontraumatic), and 14 emerged from their VS (5 nontraumatic) (table e-1 on the *Neurology*® Web site at www.neurology.org).

Forty-five patients (49%) did not show BVT (40 subacute; 24 nontraumatic). Out of these 45 patients, 8 died (5 nontraumatic), 28 remained in VS (17 nontraumatic), and 9 emerged from their VS (2 nontraumatic). Differences in outcome between patients with and without BVT were not significant. Positive predictive value of BVT on recovery from VS was only 30% while negative predictive value was 80% (table).

Discussion. Nearly half of our patients in VS showed a BVT in the absence of any other clinical sign of consciousness when assessed by means of standardized testing,[7] suggesting that BVT may be a common clinical feature of VS. In the literature, BVT is ambiguous with regard to diagnostic relevance. Some authors stated that a response to visual threat "implies awareness of threat."[2] This view seems in line with neuro-ophthalmologic studies in patients with cortical blindness, neglect, and Balint syndrome, which conclude that blinking to threat requires intact primary visual cortex as well as higher order mechanisms for visual attention thought to be mediated in the inferior parietal lobule and frontal eye fields.[3] In contrast, others suggested that "a blink response to visual threat . . . does not imply consciousness."[1] Our data support the latter view and

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table **Chi square contingency data statistics for patients in vegetative state (VS) with and without blink to visual treat**

VS with blink to visual treat (n = 46)			VS without blink to visual treat (n = 45)		
REC	VS	Died	REC	VS	Died
14 (5 NTBI)	22 (14NTBI)	10 (7NTBI)	9 (2NTBI)	28 (17NTBI)	8 (5NTBI)

Patients in VS who died, remained in VS, or recovered from VS (REC) 1 year after traumatic and 3 months after nontraumatic etiology (NTBI = nontraumatic brain injury). Positive predictive value (patients showing a blink response to visual treat who subsequently recover) 30%; negative predictive value (patients showing no blink response to visual treat who died or remained in VS) 80%. $\chi^2 = 2.018$, $p > 0.05$.

show that the presence of BVT is not a reliable predictor of recovery from VS—in contrast, its negative predictive value was 80%. BVT is commonly observed in patients who meet other requisite criteria for VS. Its presence does not necessarily herald consciousness nor recovery of consciousness in patients with severe brain injury.

e-Pub ahead of print at www.neurology.org.

From the Coma Science Group and Cyclotron Research Center (A.V., C. Schnakers, M.-A.B., O.G., S.L.) and Department of Neurology (G.M., S.L.), University of Liège, Belgium; and JFK Johnson Rehabilitation Institute (J.G., K.K., C. Smart), NJ.

Funded by the Belgian Fonds National de la Recherche Scientifique (FNRS), the French Speaking Community of Belgium Concerted Research Action, the Belgian Federal Public Service for Public Health, the European Commission, and the J.S. McDonnell Foundation. S.L. is Senior Research Associate at FNRS, and M.-A.B. and O.G. are Research Fellows at FNRS.

Disclosure: The authors report no disclosures.

Received February 6, 2008. Accepted in final form May 5, 2008.

Address correspondence and reprint requests to Pr. Steven Laureys, Coma Science Group, Cyclotron Research Center, University of Liège, Sart Tilman B30, 4000 Liège, Belgium; steven.laureys@ulg.ac.be

Copyright © 2008 by AAN Enterprises, Inc.

1. Jennett B, Cranford R, Zasler N. Consensus statement on criteria for the persistent vegetative state is being developed [letter]. BMJ 1997;314:1621–1622.
2. Wade DT, Johnston C. The permanent vegetative state: practical guidance on diagnosis and management. BMJ 1999;319:841–844.
3. Liu GT, Ronthal M. Reflex blink to visual threat. J Clin Neuro-ophthalmol 1992;12:47–56.
4. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). N Engl J Med 1994;330: 1572–1579.
5. Royal College of Physicians of London. The vegetative state: guidance on diagnosis and management. Clin Med 2003;3:249–254.
6. Australian Government National Health and Medical Research Council. Post-Coma Unresponsiveness (Vegetative State): A Clinical Framework for Diagnosis. An Information Paper. Australian Government National Health and Medical Research Council; 2003.
7. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85: 2020–2029.

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

neurocritical care society Neurocrit Care (2008) 8:262–270
DOI 10.1007/s12028-007-9016-0

ORIGINAL PAPER

Cognitive Event-Related Potentials in Comatose and Post-Comatose States

**Audrey Vanhaudenhuyse · Steven Laureys ·
Fabien Perrin**

Published online: 8 November 2007
© Humana Press Inc. 2007

Abstract We review the interest of cognitive event-related potentials (ERPs) in comatose, vegetative, or minimally conscious patients. Auditory cognitive ERPs are useful to investigate residual cognitive functions, such as echoic memory (MMN), acoustical and semantic discrimination (P300), and incongruent language detection (N400). While early ERPs (such as the absence of cortical responses on somatosensory-evoked potentials) predict bad outcome, cognitive ERPs (MMN and P300) are indicative of recovery of consciousness. In coma-survivors, cognitive potentials are more frequently obtained when using stimuli that are more ecologic or have an emotional content (such as the patient's own name) than when using classical sine tones.

Keywords Coma · Vegetative state · Minimally conscious state · ERPs · N100 · MMN · P300 · N400

Introduction

Survivors of severe traumatic or hypoxic-ischemic brain damage classically go through different clinical entities before partially or fully recovering consciousness. Consciousness is a multifaceted concept that can be divided into two main components: arousal (i.e., wakefulness, or vigilance) and awareness (e.g., awareness of the environment and of the self, thinking) [1]. Arousal is supported by several brainstem neuron populations that directly project to both thalamic and cortical neurons. Awareness is thought to be dependent upon the functional integrity of the cerebral cortex and its subcortical connections [2]. Several hypotheses attempt to explain the neuronal correlates of stimuli awareness: from a localizationist point of view to a synchronization of distant structures (see for example [3, 4]). Currently, consciousness cannot be measured objectively by any machine. Its estimation requires the interpretation of several clinical signs.

Coma is defined as a state of unarousable unresponsiveness in "which the subject lays with the eyes closed" and has no awareness of self and surroundings [1]. Coma can result from diffuse bihemispheric cortical or white-matter damage after neuronal or axonal injury, or from focal brainstem lesions that affect the pontomesenphalic tegmentum or paramedian thalami bilaterally [5]. After some days to weeks comatose patients will eventually open their eyes. When this return of 'wakefulness without awareness' is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state (VS).

The VS may be a transition to further recovery, or not. It can be diagnosed soon after a brain injury and can be partially or totally reversible or it may progress to a persistent vegetative state or death. In the VS, the brainstem is mostly spared whereas the gray or white matter of both cerebral hemispheres is widely and severely damaged. The functional preservation of the brainstem maintains arousal and autonomic functions in these patients. The other hallmark of the VS is a systematic impairment of metabolism in the polymodal associative cortices: bilateral prefrontal regions, Broca's area, parietotemporal, and posterior

A. Vanhaudenhuyse · S. Laureys
Coma Science Group, Cyclotron Research Centre and Neurology Department, University of Liège, Liege, Belgium

F. Perrin (✉)
UMR5020 "Neurosciences Sensorielles, Comportement, Cognition", Université Claude Bernard Lyon 1 – CNRS, 50, avenue Tony Garnier, 69366 Lyon cedex 07, France
e-mail: Fabien.Perrin@univ-lyon1.fr

parietal areas and precuneus (see Fig. 1 [5]). These regions are important in various functions that are necessary for consciousness, such as attention, memory, and language. In cohort studies of patients in VS, simple noxious somatosensory [6] and auditory [7, 8] stimuli have shown systematic activation of primary sensory cortices and lack of activation in higher order associative cortices from which they were functionally disconnected.

Signs of voluntary motor activity should be actively searched for in VS patients, as they herald the minimally conscious state (MCS) [9]. Functional communication indicates the next boundary—emergence from MCS—in the course of recovery. MCS describes patients who are unable to communicate, but who demonstrate inconsistent but reproducible behavioral evidence of awareness. Patients in MCS may show oriented response to noxious stimuli, sustained visual tracking, command following, intelligible verbalization, or emotional, or motor behavior that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Overall cerebral metabolism in MCS is decreased to values slightly higher but comparable to those observed in the VS (see Fig. 1). The medial parietal cortex (precuneus) and adjacent posterior cingulate cortex seem to be brain regions that differentiate patients in MCS from those in VS [5]. Interestingly, these areas are among the most active brain regions in conscious waking and are among the least active regions in altered states of consciousness such as general anesthesia, sleep, hypnotic state, dementia, and postanoxic amnesia.

Non-communicative coma survivors may show visual, motor, or verbal behaviors, which can be seen as signs of consciousness. Actually, it is very speculative to say that these behaviors are associated to some kind of consciousness. We can assert that a patient is conscious *only* when she/he communicates her/his contents of consciousness. In the absence of such reports, as it is the case in VS and MCS patients, event-related potentials (ERPs) could bring objective information on residual cerebral functioning. ERPs objectively evaluate sensory and cognitive functions at the patient's bedside offering diagnostic and prognostic value.

The ERPs Technique

The ERPs method is a derivative of the electroencephalography (EEG). The EEG, allowing recording of the spontaneous electrical brain activity, permits to identify the level of vigilance and to detect functional cerebral anomalies such as seizures or encephalopathy (i.e., exploring general physiological or pathophysiological states). However, the EEG cannot quantify the small changes induced by sensory, motor, or cognitive activities because they are buried in the recorded whole brain activity. These more subtle functional variations can be explored by averaging the EEG activity, according, for example, to the onset of a repeated stimulus. By this procedure, the activity time-locked to the stimulus is revealed and the spontaneous brain activity cancels out, simply for statistical reasons (see Fig. 2). This technique, called ERPs, reveals voltage deflexions (or components or potentials) indexing the successive activation of the nervous structures implied in the studied sensory, motor, or cognitive paradigms. ERPs, obtained in response to a sensory stimulation, reflect the time course of information processing from "low-level" peripheral receptive structures to "high-order" associative cortices. Short-latency ERPs, or exogenous ERP components (ranging from 0 to 100 ms), correspond to the activation of the ascending pathways to the primary cortex. Cognitive ERPs, or endogenous ERP components (obtained after 100 ms), reflect both sub-cortical and cortical structures, including associative areas. While, short-latency ERPs are affected by the physical properties of the stimulus, cognitive ERPs depend on the psychological significance of the stimulus and are linked to the experimental condition and the level of arousal or attention.

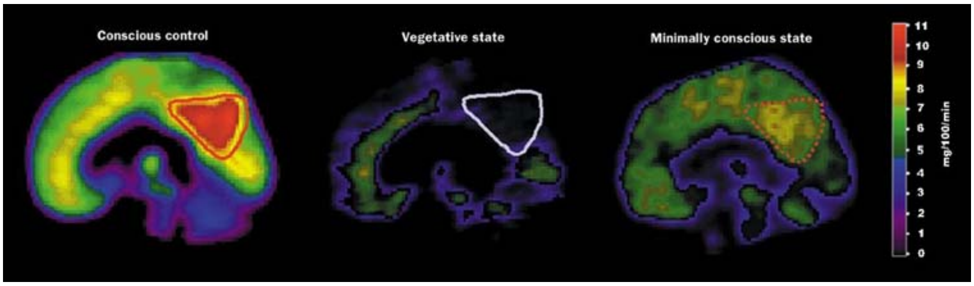


Fig. 1 Metabolism in healthy participants, VS and MCS patients. Sagittal images of resting cerebral metabolism in healthy participants (left part of the figure), in patients in a VS (middle part) and in patients in minimally conscious state (right part). Mg glucose metabolized per 100 g of brain tissue per minute (adapted from Laureys et al. [5])

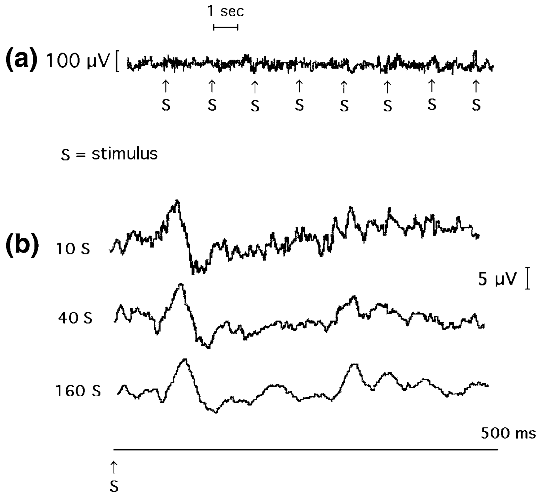


Fig. 2 Event-related potentials principles. Electroencephalographic (EEG) activity is recorded by scalp electrodes and stimuli are presented several times (a). By merging epochs of EEG, according to the beginning of a stimulus, the activity time-locked to the stimulus is revealed and the spontaneous brain activity cancels. The more stimuli presented the more spontaneous brain activity cancels simply for statistical reasons (b) (adapted from Guérit et al. [10])

Predicting Values of ERPs

Predicting functional outcome after coma is an important aspect of intensive care. Predicting values of ERPs are estimated by calculating the relationship between the presence (or the absence) of a component and the outcome of patients. Positive predictive value for favorable outcome (PV+) estimates the percentage of patients who will recover when a component is evoked (it is the number of patients with favorable outcome and with the component/total number of patients with the component). In contrast, positive predictive value for unfavorable outcome (PV−) estimates the percentage of patients who won't recover when no component is evoked (it is the number of patients with unfavorable outcome and without the component/total number of patients without the component). The relationship between ERPs and outcome could be also assessing from the outcome. Sensitivity for unfavorable outcome (or specificity for favorable outcome; Sp+) estimates the percentage of patients who had not a component when the outcome is bad (it is the number of patients with unfavorable outcome and without the component/total number of patients with unfavorable outcome). In contrast, sensitivity for favorable outcome (or specificity for unfavorable outcome; Sp−) estimates the percentage of patients who had a component when the outcome is good (it is the number of patients with favorable outcome and with the component/total number of patients with favorable outcome).

Short-Latency ERPs

Short-latency ERPs are routinely used because they are a validated means to predict poor outcome (for a recent review, see Laureys et al. [11]). They show a very low rate of false-negative predictions, i.e., most patients bilaterally missing these potentials show a negative prediction outcome. On the other hand, the rate of false-positive predictions is high, i.e., well-preserved potentials are recorded in patients who have a bad clinical prognosis. If both somatosensory (i.e., repeated electrical stimulation of the median nerve at the wrists) and auditory stimulations (i.e., presentation of "clicks" using headphones) have been used, they bring relatively similar conclusions. Visual ERPs (using goggles with flashing LEDs) are of limited use at the intensive care setting because they fail to show systematic activation even in healthy subjects.

A recent meta-analysis confirmed that somatosensory evoked-potentials (SEPs), which reflect the activation of the subcortical somatosensory pathways and of the primary somatosensory cortex, are superior, with few exceptions, to pupillary responses, motor responses, Glasgow Coma Scale, EEG, and computed tomography for the prediction of favorable or unfavorable outcome after acute severe brain damage [12]. Bilateral absence of SEPs among patients in coma is strongly associated with a non-awakening prognosis (PV− near 100%), i.e., death or permanent VS [13–16]. At the same time, all patients with favorable outcome have developed normal SEPs (Sp− near 100%). In contrast, normal SEPs are associated to a great number of false positives (for reviews see [13, 17–19]) suggesting that SEPs are not a good predictor of recovery.

The absence of brainstem auditory-evoked potentials (BAEPs), which are evoked in the first 10 ms and reveal the activity from the auditory nerve to the inferior colliculus [20], can be seen as a reliable prognosticator for poor outcome when there is no evidence of peripheral auditory damage. On the other hand, the presence of normal BAEPs does not reliably indicate a good outcome [10, 13, 21–23]. Similarly, the absence of middle-latency auditory-evoked potentials (MLAEPs; appearing between 10 and 50 ms and probably signing the activation of thalamus and primary auditory cortex) is strongly associated with bad outcome in postanoxic coma [23–25].

Cognitive ERPs

If short-latency ERPs are useful to predict unfavorable outcomes in coma survivors, they are less helpful in prognosticating recovery. Moreover, they only estimate the integrity of ascending pathways and not of possible residual cognitive functioning. Some recent studies suggest that the

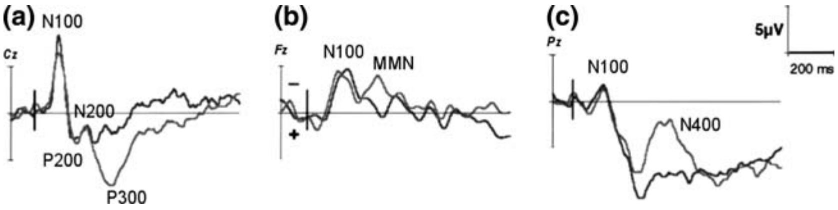


Fig. 3 Auditory cognitive ERPs in healthy participants. (**a**) In oddball paradigms, monotonous stimuli (gray trace) elicit the N100, P200 waves, and deviant stimuli (dark trace) elicit the N100, P200, N200, and P300 waves (note that P200 and N200 waves were not systematically investigated in patients with disorders of consciousness). (**b**) In inattentive oddball paradigms, a MMN is evoked by the deviant stimulus (dark trace), following the N100 wave. (**c**) Incongruous words (dark trace) elicit N100 and N400 components whereas congruous words do not elicit the N400 component

use of auditory cognitive ERPs might complement short-latency ERPs evaluation at the intensive care unit. As compared to early ERPs, cognitive ERPs are very dependent on the experimental conditions. Thus, it is very important to perform clinical explorations in optimal vigilance, attention, and habituation settings. This implies to use a number of stimuli which is optimized to both dig up ERPs from the background EEG activity and to avoid habituation phenomena. Since all published studies are not conducted in similar conditions, the results are not homogenous.

We reviewed Medline from January 1, 1980 to June 1, 2007 (search terms: coma, outcome, and evoked potentials) and selected all studies investigating cognitive ERPs (N100, MMN, P300, or N400) of comatose and post-comatose (VS and MCS) patients, and in which prognostic values were described.

The N100 Component

The N100 wave is a negative deflection, elicited around 100 ms, in response to any auditory stimulus (see Fig. 3a–c) [26]. It corresponds to the activation of the auditory cortex (and perhaps also of dorsolateral prefrontal areas) [27–29].

If the presence of a N100 in comatose and post-comatose patients suggests that the primary auditory cortex is functionally preserved, it does not appear to be a good predictor of bad or good outcome (see Fig. 4). Some authors suggest that its presence predicts (see predictive values of N100 in Table 1) recovery [23, 34, 35] while others do not [31–33]. On the other hand, two studies suggest that its absence appears to be a good predictor of bad outcome and that, among patients who recovered, a high proportion of them had a N100 [31, 32].

The Mismatch Negativity (MMN)

The MMN is a negative component elicited after 100–200 ms by any change or 'mismatch,' in a sequence of monotonous auditory stimuli (i.e., an 'oddball paradigm') in inattentive subjects—who for example watch TV (see Fig. 3b) [41, 42]. It is relatively small in amplitude; thus it is generally displayed as a difference wave computed by subtracting the repetitive from the deviant response. For the auditory modality, the primary auditory cortex and prefrontal areas participate to its generation [43, 44]. MMN may index an automatic stage of information processing after a comparison process between the afferent input and a memory trace developed by the repetitive stimulation [45].

Data on MMN in comatose patients converge to the conclusion that it is a very good predictor of recovery (see Table 1 for predictive values of MMN), notably in anoxic coma [36, 46]. In a prospective cohort study on 346 comatose patients, Fischer et al. [23, 25, 35] reported a high prognostic value of the MMN for recovery, all etiology confounded (see Fig. 4). In both groups, a very high proportion of patients who did not recover did not evoke a MMN component but low Sp− and PV− were also observed. Similar results have been obtained, more recently, by Naccache et al. [47].

Kotchoubey et al. found a MMN in 65% of patients in VS and in 34% of patients in MCS [48, 49]. Interestingly, they showed that complex tones elicited a MMN significantly more frequently (in 50% of patients) than pure tones (24%). Very recently, a correlation has been found between

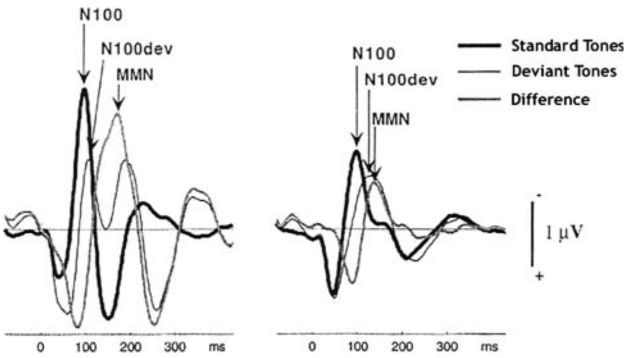


Fig. 4 Auditory cognitive ERPs in comatose patients. N100 and MMN components are elicited both in healthy subjects (left part of the figure) and in comatose patients, with GCS $\leq$ 8 (right part) adapted from Fischer et al. [30]

Table 1 Predictive values of cognitive ERPs (in %)

	Authors	Number of patients	PV+, rate % (95% CI)	PV−, rate % (95% CI)	Sp+, rate % (95% CI)	Sp−, rate % (95% CI)
N100	Mutschler et al. [31]	20	40 (12–73)	**100** (69–100)	63 (35–85)	**100** (40–100)
	Glass et al. [32]	8	29 (4–71)	**100** (2–100)	17 (0–64)	**100** (16–100)
	Guérit et al. [33]	103	77 (66–87)	54 (43–65)	56 (45–67)	76 (65–85)
	Mazzini et al. [34]	21	**83** (58–95)	41 (22–66)	**83** (58–95)	41 (22–66)
	Fischer et al. [35]	346	**80** (74–86)	48 (40–56)	65 (55–73)	67 (61–73)
MMN	Kane et al. [36]	54	**100** (86–100)	45 (27–64)	**100** (77–100)	56 (40–72)
	Fischer et al. [35]	346	**89** (80–94)	38 (32–44)	**91** (83–95)	33 (27–39)
P300	Yingling et al. [37]	8	**100** (16–100)	75 (35–97)	**100** (54–100)	50 (7–93)
	Gott et al. [38]	20	**83** (36–99)	71 (42–92)	**91** (59–99)	56 (21–86)
	Rappaport et al. [39]	8	**88** (47–99)	**100** (2–100)	50 (1–99)	**100** (54–100)
	DeGiorgio et al. [17]	20	**83** (36–99)	71 (42–92)	**91** (59–99)	56 (21–86)
	Mutschler et al. [31]	20	50 (12–88)	**93** (66–99)	81 (54–96)	75 (19–99)
	Guérit et al. [33]	103	**100** (96–100)	41 (30–52)	**100** (96–100)	18 (10–28)
	Signorino et al. [40]	25	**87** (60–98)	50 (19–81)	71 (29–96)	72 (47–90)
	Glass et al. [32]	8	33 (4–78)	**100** (16–100)	33 (4–77)	**100** (16–100)
	Mazzini et al. [34]	21	58 (34–78)	0 (0–16)	**83** (58–95)	0 (0–16)
	Lew et al. [14]	22	71 (29–96)	**87** (59–98)	**87** (60–98)	71 (29–96)

Positive predictive value for favorable (PV+) and unfavorable outcome (PV-), and sensitivity for unfavorable (Sp+) and favorable outcome (Sp-) are reported for articles in which these values were reported. Values in bold are superior to 80%

MMN amplitude and clinical diagnosis: Wijnen et al. showed, in 10 vegetative patients, that MMN amplitude increases with recovery to consciousness, i.e., when patients reached a MCS [50].

The P300 Wave

The P300 response is a positive wave which is elicited, around 300 ms post-stimulus, when subjects detect a rare and unpredictable target stimulus in a regular train of standard stimuli, i.e., in the oddball paradigm (see Fig. 3a) [51]. This potential is larger when the probability of occurrence of the target stimulus decreases [52]. The P300 response is composed by two "sub-components" modulated differentially by experimental manipulations: the P3a peaks near 250 ms (and has maximal frontal topography) and the P3b peaks near 350 ms (and has maximal parietal topography) [53]. The P3a amplitude is quite similar in active or passive attentional tasks (in the second, it follows the MMN) whereas P3b is larger in active oddball tasks, suggesting that the P3a is more sensitive to involuntary detection and P3b to attentional discrimination. However, P3b is still elicited in passive paradigms [54] and its amplitude is particularly large when the deviant stimulus is salient for the subject, for instance presenting the own name as compared to other names [55, 56]. This suggests that P3b is not only dependent on the subject's attention but also on the importance of the stimulus for the subject. This latter property is very helpful for the investigation of non-communicating patients, as we will see in the next paragraph. The P300 can be seen as a post-decisional process since it follows the EMG response of the stimulus detection [57]. Furthermore, it would reflect the closure of the cognitive period following the identification of the stimulus [58]. Multiple intracranial generators have been postulated for the auditory P300: medial (hippocampal) and lateral sources of the temporal cortex, as well as thalamic, parietal, and prefrontal generators [59–62].

In most studies the presence of a P300 correlates with favorable outcome in comatose patients (see predictive values of P300 in Table 1). However, the data are not systematically convergent. While a great number of studies suggest, as MMN data, that among patients who developed a P300 wave a high proportion of them recovered [17, 33, 37, 38], others do not [31, 63]. This variability could be explained by the limited number of patients studied, as well as the limited number of patients evoking a P3 response to deviant tones.

The use of emotional stimuli increases the percentage of traumatic comatose patients exhibiting P300 activity, and helps to investigate more ecological functions. Signorino et al. used both a conventional oddball paradigm and an oddball paradigm in which the tones were coupled to emotional verbal stimuli (i.e., a short phrase spoken by a member of the family or the patient's name) and obtained a

P300 in 36–38% of comatose patients in the first condition and in 52–56% in the second condition [40, 64]. In their studies, a high proportion of patients evoking a P300 recovered. Lew et al. confirmed that an emotional stimuli (presenting "mommy") evoke larger P300 than tones [14, 65]. They confirmed that the presence of the P300 component is more associated to good outcome than SEPs, but also that its absence is associated with a bad outcome (for Glasgow Outcome Scale between 1 and 4).

For post-comatose patients, two studies report a few number of patients evoking a P300 wave in response to deviant tones, and suggest that P300 is a very good indicator for poor outcome [32, 39]. However, these results have to be interpreted very carefully since only a small cohort of patients was investigated.

The chance to observe a cerebral response in VS and MCS patients could be increased by the use of more ecological or salient stimuli. Kotchoubey et al. showed that P300 is elicited more often in response to complex tones (i.e., more harmonic sounds) than to simple tones (in respectively 22% vs. 15% in VS and in 31% vs. 8% in MCS) [66, 67]. Emotional stimuli, such as the patient's own name, also increase the number of reactive patients [34, 68–70]. We have previously shown that the P300 component can be observed in response to the patient's name in MCS and VS patients, the latter failing to subsequently recover [71] (see Fig. 5). These results suggest that partially preserved verbal processing could be observed in non-communicative brain damaged patients, notably for the detection of very salient stimuli, such as the subject's own name (this function appearing delayed in MCS and in VS patients).

The N400 Potential

The N400 is a negative potential, occurring around 400 ms, which is larger in response to verbal stimuli that are discordant (phonologically or semantically) with respect to a preceding verbal stimulus or sentence, than that evoked by concordant verbal stimuli (see Fig. 3c) [72]. It is possible to observe the occurrence of the N400 when subjects have to direct their attention away from the semantic aspect of the stimulus [73–75], suggesting that it reflects in part automatic processes. Medial and lateral temporal cortex, as well as the left frontal and parietal cortex, seem to participate to its generation [62, 76, 77].

Schoenle and Witzke [78] recorded ERPs in response to sentences ending with semantically congruent and incongruent words in post-comatose patients. A N400 response to incongruous words was reported in some VS patients (12%) and in a majority (77%) of 'near-VS' patients (the authors used this term for patients with signs of habituation, orienting reactions, or visual fixation or pursuit), and in nearly all (90%) of the patients who are not in a VS (showing 'some meaningful behavior,' i.e., probably in MCS). This confirms that semantic processes are relatively preserved in a majority of MCS patients but probably not preserved in a great number of VS patients. Unfortunately, these authors did not report its prognostic value.

Conclusions

This review shows that cognitive ERPs are of interest in the clinical investigation of comatose and post-comatose states. While early ERPs (such as SEPs) are very good prognosticators of bad outcome, cognitive ERPs appear to be good predictors of favorable outcome (notably MMN and P300). Moreover, cognitive ERPs are very helpful to estimate the residual cognitive functions of comatose and post-comatose patients. They suggest the integrity of echoic memory (MMN), of acoustical and semantic discrimination (P300), or incongruent language detection (N400) in some of them.

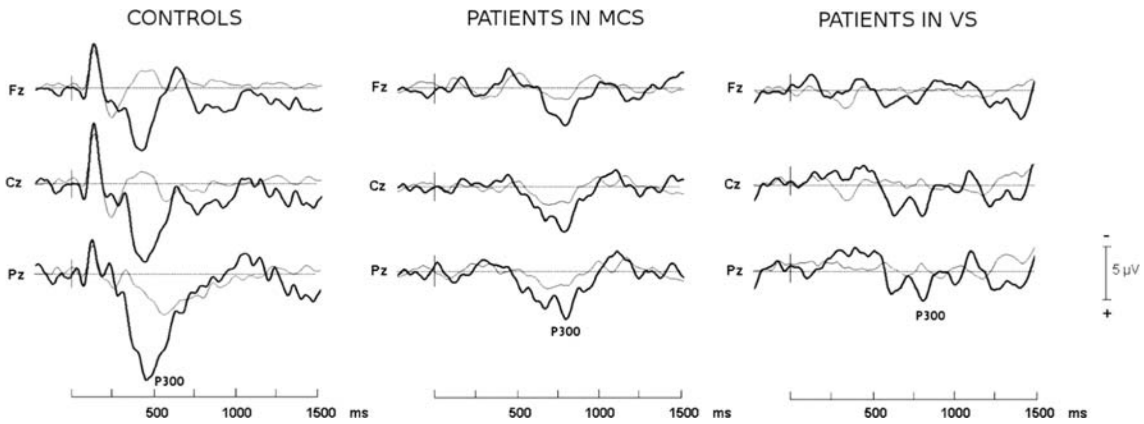


Fig. 5 ERPs to patient's name. ERPs to the subject's own name (dark trace) and to other first names (gray trace) in control subjects, in patients in a minimally conscious state and those in a vegetative state

They also show that stimuli which are more ecologic or have an emotional content increase the chance to record a cerebral response as compared to classical neutral tones.

It should be noted that results among cognitive ERP studies were heterogeneous. This could be explained in part by differences in technique, level of consciousness and muscle artifacts when tested, small numbers of patients, and varying patients' etiologies (anoxic-ischemic vs. traumatic etiology). In our view, it is not yet warranted to conclude on the true prognostic value of cognitive ERPs in neurocritical care. Before firm conclusions can be drawn, it is necessary to obtain data on large homogenous populations, to use robust recording conditions, and to more systematically investigate differences between anoxic-ischemic vs. traumatic brain damage. This would help to make a clear classification between etiology, cognitive ERPs, and outcome.

Accurate patients' classification and better prognostic indications would also be obtained by longitudinal studies (i.e., by the systematic investigation of all cognitive ERPs in one patient). This would be helpful to investigate, for example, the temporal dynamics of each ERP wave in comatose and post-comatose states. For example, it can be hypothesized that in coma survivors MMN components would appear first, followed by P300 and next followed by N400 waves, appearing first for words and later for sentences. It is likely that patients with a similar diagnosis would not all be able to evoke the same number of ERP components. Longitudinal investigations could identify predictors of good functional outcome, i.e., whether recovery from coma will be limited to a MCS (e.g., if a P300 wave is observed) or to full consciousness (e.g., if a N400 wave for sentences is observed). Currently, validated reliable and easily available makers of good functional outcome in coma are awaited to further improve the management of patients surviving severe brain damage.

At last, when cognitive ERPs method will become a routinely used tool in intensive care unit, it will be very important to combine ERPs technique with functional neuroimagery to delineate both electrophysiological and anatomical basis of recovery in brain injury.

References

1. Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: Davis, F.A; 1983.
2. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci 2005;9(12):556–9.
3. Rees G, Wojciulik E, Clarke K, Husain M, Frith C, Driver J. Neural correlates of conscious and unconscious vision in parietal extinction. Neurocase 2002;8(5):387–93.
4. Dehaene S, Changeux J. Neural mechanisms for access to consciousness. In: Gazzaniga, M, editor. The cognitive neurosciences III. Cambridge: MIT Press; 2004.
5. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3(9): 537–46.
6. Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17(2):732–41.
7. Boly M, Faymonville ME, Peigneux P, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 2004;61(2):233–8.
8. Laureys S, Faymonville ME, Degueldre C, et al. Auditory processing in the vegetative state. Brain 2000;123(Pt 8):1589–601.
9. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58(3): 349–53.
10. Guerit JM, de Tourtchaninoff M, Soveges L, Mahieu P. The prognostic value of three-modality evoked potentials (TMEPs) in anoxic and traumatic comas. Neurophysiol Clin 1993;23 (2–3):209–26.
11. Laureys S, Perrin F, Schnakers C, Boly M, Majerus S. Residual cognitive function in comatose, vegetative and minimally conscious states. Curr Opin Neurol 2005;18(6):726–33.
12. Carter BG, Butt W. A prospective study of outcome predictors after severe brain injury in children. Intensive Care Med 2005;31:840–5.
13. Cant BR, Hume AL, Judson JA, Shaw NA. The assessment of severe head injury by short-latency somatosensory and brainstem auditory evoked potentials. Electroencephalogr Clin Neurophysiol 1986;65(3):188–95.
14. Lew HL, Dikmen S, Slimp J, et al. Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. Am J Phys Med Rehabil 2003;82:53–61.
15. Logi F, Fischer C, Murri L, Mauguiere F. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 2003;114(9): 1615–27.
16. Robinson LR, Micklesen PJ, Tirschwell DL, Lew HL. Predictive value of somatosensory evoked potentials for awakening from coma. Crit Care Med 2003;31(3):960–7.
17. De Giorgio CM, Rabinowicz AL, Gott PS. Predictive value of P300 event-related potentials compared with EEG and somatosensory evoked potentials in non-traumatic coma. Acta Neurol Scand 1993;87(5):423–7.
18. Amantini A, Grippo A, Fossi S, et al. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. Neurophysiol Clin 2005;116:229–35.
19. Carter BG, Butt W. Review of the uses of somatosensory evoked potentials in the prediction of outcome after severe brain injury. Crit Care Med 2001;29(1):178–86.
20. Picton TW, Hillyard SA, Krausz HI, Galambos R. Human auditory evoked potentials. I. Evaluation of components. Electroencephalogr Clin Neurophysiol 1974;36(2):179–90.
21. Fischer C, Ibanez V, Jourdan C, Grau A, Mauguiere F, Artru F. Early and middle latency auditory evoked potentials and somatosensory evoked potentials in the vital and functional prognosis of severe brain injuries in intensive care. Agressologie 1988;29(5):359–63.
22. Garcia-Larrea L, Artru F, Bertrand O, Pernier J, Mauguiere F. The combined monitoring of brain stem auditory evoked potentials and intracranial pressure in coma. A study of 57 patients. J Neurol Neurosurg Psychiatry 1992;55(9):792–8.
23. Fischer C, Luaute J, Salord F, Jourdan C, Morlet D. Valeur pronostique des PEA au stade aigu du coma. PE auditifs précoces, de latence moyenne, tardifs et négativité de discordance (MMN).

In: Guérit JM, editor. L'évaluation neurophysiologique des comas, de la mort encéphalique et des états végétatifs. Solal ed. Marseille; 2001. p. 169–81.

24. Litscher G, Schwarz G, Kleinert R. Brain-stem auditory evoked potential monitoring. Variations of stimulus artifact in brain death. Electroencephalogr Clin Neurophysiol 1995;96(5):413–9.
25. Fischer C, Luaute J, Némoz C, Morlet D, Kirkorian G, Mauguière F. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Crit Care Med 2006;34:1520–4.
26. Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. Science 1973;182(108): 177–80.
27. Liegeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. Electroencephalogr Clin Neurophysiol 1994;92(3):204–14.
28. Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987;24(4):375–425.
29. Scherg M, Von Cramon D. Two bilateral sources of the late AEP as identified by a spatio-temporal dipole model. Electroencephalogr Clin Neurophysiol 1985;62(1):32–44.
30. Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. Clin Neurophysiol 1999;110:1601–10.
31. Mutschler V, Chaumeil CG, Marcoux L, Wioland N, Tempe JD, Kurtz D. [Auditory P300 in subjects in a post-anoxic coma. Preliminary data]. Neurophysiol Clin 1996;26(3):158–63.
32. Glass I, Sazbon L, Groswasser Z. Mapping "cognitive" event-related potentials in prolonged postcoma unawareness state. Clin Electroencephalogr 1998;29(1):19–30.
33. Guerit JM, Verougstraete D, de Tourtchaninoff M, Debatisse D, Witdoeckt C. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. Clin Neurophysiol 1999;110:1260–9.
34. Mazzini L, Zaccala M, Gareri F, Giordano A, Angelino E. Long-latency auditory-evoked potentials in severe traumatic brain injury. Arch Phys Med Rehabil 2001;82(1):57–65.
35. Fischer C, Luaute J, Adeleine P. Predictive value of sensory and cognitive evoked potentials for awakening from coma. Neurology 2004;63:669–73.
36. Kane NM, Curry SH, Rowlands CA, et al. Event-related potentials–neurophysiological tools for predicting emergence and early outcome from traumatic coma. Intensive Care Med 1996;22(1):39–46.
37. Yingling CD, Hosobuchi Y, Harrington M. P300 as a predictor of recovery from coma. Lancet 1990;336(8719):873.
38. Gott PS, Rabinovicz AL, DiGiorgio CM. P300 auditory event-related potentials in nontraumatic coma: association with Glasgow Coma Score and awakening. Arch Neurol 1991;48:1267–70.
39. Rappaport M, McCandless K, Pond W, Krafft MC. Passive P300 response in traumatic brain injury patients. J Neuropsychiatry Clin Neurosci 1991;3:180–5.
40. Signorino M, D'Acunto S, Cercaci S, Pietropaoli P, Angeleri F. The P300 in traumatic coma: conditioning of the odd-ball paradigm. J Psychophysiol 1997;11:59–70.
41. Naatanen R, Gaillard AW, Mantysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst) 1978;42(4):313–29.
42. Naatanen R, Lehtokoski A, Lennes M, et al. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature 1997;385(6615):432–4.
43. Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear 1995;16(1):38–51.
44. Celsis P, Boulanouar K, Doyon B, et al. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. Neuroimage 1999;9(1):135–44.
45. Naatanen R. Attention and brain function. Hillsdale: Erlbaum; 1992.
46. Kane NM, Curry SH, Butler SR, Cummins BH. Electrophysiological indicator of awakening from coma. Lancet 1993;341:688.
47. Naccache L, Puybasset L, Gaillard R, Serve E, Willer JC. Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure. Clin Neurophysiol 2005;116(4):988–9.
48. Kotchoubey B, Lang S, Herb E, et al. Stimulus complexity enhances auditory discrimination in patients with extremely severe brain injuries. Neurosci Lett 2003;352(2):129–32.
49. Kotchoubey B, Lang S, Mezger G, et al. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin Neurophysiol 2005;116(10):2441–53.
50. Wijnen VJ, van Boxtel GJ, Eilander HJ, de Gelder B. Mismatch negativity predicts recovery from the vegetative state. Clin Neurophysiol 2007;118(3):597–605.
51. Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. Science 1965;150(700):1187–8.
52. Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol 1992;9(4):456–79.
53. Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 1975;38(4):387–401.
54. Polich J. Frequency, intensity, and duration as determinants of P300 from auditory stimuli. J Clin Neurophysiol 1989;6(3):277–86.
55. Berlad I, Pratt H. P300 in response to the subject's own name. Electroencephalogr Clin Neurophysiol 1995;96(5):472–4.
56. Perrin F, Garcia-Larrea L, Mauguiere F, Bastuji H. A differential brain response to the subject's own name persists during sleep. Clin Neurophysiol 1999;110(12):2153–64.
57. Goodin DS, Aminoff MJ. The relationship between the evoked potential and brain events in sensory discrimination and motor response. Brain 1984;107(Pt1):241–51.
58. Verleger R. The true P3 is hard to see: some comments on Kok's (1986) paper on degraded stimuli. Biol Psychol 1988;27(1): 45–50.
59. Baudena P, Halgren E, Heit G, Clarke JM. Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 1995;94(4):251–64.
60. Halgren E, Baudena P, Clarke JM, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 1995;94(4):229–50.
61. Halgren E, Baudena P, Clarke JM, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr Clin Neurophysiol 1995;94(3):191–220.
62. Smith ME, Stapleton JM, Halgren E. Human medial temporal lobe potentials evoked in memory and language tasks. Electroencephalogr Clin Neurophysiol 1986;63(2):145–59.
63. Harris DP, Hall JW, 3rd. Feasibility of auditory event-related potential measurement in brain injury rehabilitation. Ear Hear 1990;11(5):340–50.
64. Signorino M, D'Acunto S, Angeleri F, Pietropaoli P. Eliciting P300 in comatose patients. Lancet 1995;345(8944):255–6.
65. Lew HL, Slimp J, Price R, Massagli TL, Robinson LR. Comparison of speech-evoked v tone-evoked P300 response: implications for predicting outcomes in patients with traumatic brain injury. Am J Phys Med Rehabil 1999;78(4):367–71.

66. Kotchoubey B, Lang S, Bostanov V, Birbaumer N. Is there a mind? Electrophysiology of unconscious patients. News Physiol Sci 2002;17:38–42.
67. Kotchoubey B, Lang S. Event-related potentials in an auditory semantic oddball task in humans. Neurosci Lett 2001;310(2–3): 93–6.
68. Marosi M, Prevec T, Masala C, et al. Event-related potentials in vegetative state. Lancet 1993;341(8858):1473.
69. Giorgianni R, Lo Presti R, D'Aleo G, Mondo N, Di Bella P, Bramanti P. Event-related potentials in patients in persistent vegetative state. EEG J 1997;103(1):149.
70. Prevec T, Saltuari L, Masala C. Mental functions in apallic patients after traumatic cerebral lesions. Electroencephalogr Clin Neurophysiol 1993;87:S130.
71. Perrin F, Schnakers C, Schabus M, et al. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol 2006;63(4):562–9.
72. Kutas M, Hillyard SA. Reading senseless sentences: brain potentials reflect semantic incongruity. Science 1980;207(4427): 203–5.
73. Connolly JF, Stewart SH, Phillips NA. The effects of processing requirements on neurophysiological responses to spoken sentences. Brain Lang 1990;39(2):302–18.
74. Kutas M, Hillyard SA. An electrophysiological probe of incidental semantic association. J Cogn Neurosci 1989;1:38–49.
75. Perrin F, Garcia-Larrea L. Modulation of the N400 potential during auditory phonological/semantic interaction. Brain Res Cogn Brain Res 2003;17(1):36–47.
76. Hagoort P, Brown CM, Swaab TY. Lexical-semantic event-related potential effects in patients with left hemisphere lesions and aphasia, and patients with right hemisphere lesions without aphasia. Brain 1996;119(Pt 2):627–49.
77. McCarthy G, Nobre AC, Bentin S, Spencer DD. Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. J Neurosci 1995;15(2):1080–9.
78. Schoenle PW, Witzke W. How vegetative is the vegetative state? Preserved semantic processing in vegetative state patients: evidence from N400 event related potentials. Neurorehabilitation 2004;19:329–34.

Brain Advance Access published December 23, 2009

doi:10.1093/brain/awp313

BRAIN
A JOURNAL OF NEUROLOGY

Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients

Audrey Vanhaudenhuyse,[1,*] Quentin Noirhomme,[1,*] Luaba J.-F. Tshibanda,[1,2] Marie-Aurelie Bruno,[1] Pierre Boveroux,[1,3] Caroline Schnakers,[1] Andrea Soddu,[1] Vincent Perlbarg,[4] Didier Ledoux,[1,3] Jean-François Brichant,[3] Gustave Moonen,[5] Pierre Maquet,[1] Michael D. Greicius,[6] Steven Laureys[1,5] and Melanie Boly[1,5]

1 Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
2 Department of Radiology, CHU Sart Tilman Hospital, University of Liège, Belgium
3 Department of Anaesthesiology, CHU Sart Tilman Hospital, University of Liège, Belgium
4 Inserm, U678, Hopital La Pitié-Salpêtrière, Paris, France
5 Department of Neurology, CHU Sart Tilman Hospital, University of Liège, Belgium
6 Functional Imaging in Neuropsychiatric Disorders (FIND) Lab, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, USA

*These authors contributed equally to the work.

Correspondence to: Mélanie Boly,
Coma Science Group,
Cyclotron Research Centre,
University of Liège,
Allée du 6 août, B30,
Liège, Belgium
E-mail: mboly@student.ulg.ac.be

Correspondence may also be addressed to: Steven Laureys,
Coma Science Group,
Cyclotron Research Centre,
University of Liège,
Allée du 6 août, B30,
Liège, Belgium
E-mail: steven.laureys@ulg.ac.be

The 'default network' is defined as a set of areas, encompassing posterior-cingulate/precuneus, anterior cingulate/mesiofrontal cortex and temporo-parietal junctions, that show more activity at rest than during attention-demanding tasks. Recent studies have shown that it is possible to reliably identify this network in the absence of any task, by resting state functional magnetic resonance imaging connectivity analyses in healthy volunteers. However, the functional significance of these spontaneous brain activity fluctuations remains unclear. The aim of this study was to test if the integrity of this resting-state connectivity pattern in the default network would differ in different pathological alterations of consciousness. Fourteen non-communicative brain-damaged patients and 14 healthy controls participated in the study. Connectivity was investigated using probabilistic independent component analysis, and an automated template-matching component selection approach. Connectivity in all default network areas was found to be negatively correlated with the degree of clinical consciousness impairment, ranging

---

Received July 17, 2009. Revised October 20, 2009. Accepted October 21, 2009.
© The Author (2009). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.
For Permissions, please email: journals.permissions@oxfordjournals.org

from healthy controls and locked-in syndrome to minimally conscious, vegetative then coma patients. Furthermore, precuneus connectivity was found to be significantly stronger in minimally conscious patients as compared with unconscious patients. Locked-in syndrome patient's default network connectivity was not significantly different from controls. Our results show that default network connectivity is decreased in severely brain-damaged patients, in proportion to their degree of consciousness impairment. Future prospective studies in a larger patient population are needed in order to evaluate the prognostic value of the presented methodology.

Keywords: Default mode; fMRI; coma; vegetative state; minimally conscious state

Abbreviations: CRS-R = Coma Recovery Scale-Revised; DMN = default mode network; fMRI = functional magnetic resonance imaging; PCC = posterior cingulate cortex

Introduction

In recent years, advances in emergency medicine and reanimation have considerably increased the number of patients surviving prolonged cardiac arrest or severe motor vehicle accidents (Laureys and Boly, 2008). An important proportion of these surviving patients are left with severe brain damage, leading to the presence of disorders of consciousness. Among disorders of consciousness, coma is defined by 'unarousable unresponsiveness'; and 'vegetative state' by preserved behavioural sleep–wake cycles and reflexive but not purposeful behaviours (Laureys and Boly, 2007). Minimally conscious patients, though unable to communicate, show inconsistent non-reflexive behaviours, interpreted as signs of awareness of self or environment (Giacino *et al.*, 2002). The locked-in syndrome describes patients who are awake and conscious but have no means of producing speech, limb or facial movements (American Congress of Rehabilitation Medicine, 1995). A particular problem in patients with disorders of consciousness is that the clinical diagnosis is very challenging at the bedside, and several studies have reported high rates of misdiagnosis, reaching up to 40% (Majerus *et al.*, 2005; Schnakers *et al.*, 2009). It is now increasingly recognized that diagnosing these distinct conditions correctly is critical, both for ethical reasons and in order to improve the clinical management of these patients. Indeed, several studies have shown that brain activation in response to auditory or painful stimuli is very limited when in a vegetative state, while this activation is virtually normal in patients who are minimally conscious (Boly *et al.*, 2004, 2008*a*), suggesting the possibility of residual external stimuli perception in the latter patient population. Furthermore, preliminary data show that patients in the minimally conscious state have a much better functional prognosis than patients in a vegetative state, independently of the aetiology (Giacino, 2005). These concerns raise the need for reliable paraclinical markers as a complement to the clinical assessment in differentiating patients in a vegetative state from patients in a minimally conscious state.

Over the last 8 years, increasing attention has been paid to the study of spontaneous brain activity and its significance for cognition and behaviour (Raichle, 2006). In particular, the concept of a 'default mode network (DMN) of brain function' was introduced by Raichle *et al.* (2001), after observing that a number of areas including the precuneus, bilateral temporo-parietal junctions and medial prefrontal cortex, were more active at rest than when the subjects were involved in an attention-demanding cognitive task. This network of areas, now commonly referred to as the 'DMN', has been replicably implicated in cognitive processes like 'day-dreaming' or 'mind-wandering', stimulus-independent thoughts or self-related thoughts (Laureys *et al*., 2007; Mason *et al*., 2007; Buckner *et al*., 2008). Though the functional significance of the DMN remains a matter of debate, it has been suggested as a candidate for the network subserving basic functions related to consciousness (Boly *et al*., 2008*b*; Greicius *et al.*, 2008). Studying this network in patients with disorders of consciousness is, at first glance, a very challenging undertaking, due to the highly subjective and complex cognitive functions reported to be supported by this network.

Several studies in healthy volunteers have shown the ability of resting state functional magnetic resonance imaging (fMRI) to identify structured patterns of functional connectivity among defined neuroanatomical systems reliably, including the DMN (Cavanna and Trimble, 2006; Damoiseaux *et al*., 2006; Cavanna, 2007; Shehzad *et al*., 2009). Of potentially major interest from the clinical point of view, is the fact that resting state fMRI connectivity studies allow the investigation of higher order cognitive networks like the DMN, without requiring the patients' collaboration. This fact is particularly important in non-communicative patients such as those with disorders of consciousness. Resting state fMRI acquisitions are also very easy to perform compared with standard task-based fMRI paradigms, and could thus have a potentially broader and faster translation into clinical practice. However, to date, the functional significance of resting state connectivity patterns remain unclear. Some authors have even questioned the value and interpretability of spontaneous brain activity fluctuations as recorded by fMRI (Morcom and Fletcher, 2007).

The aim of this study was to investigate DMN resting state fMRI connectivity in a cohort of patients with disorders of consciousness including coma, vegetative state, minimally conscious state and locked-in syndrome. We hypothesized that DMN connectivity strength would be related to the level of consciousness of non-communicative brain-damaged patients, as assessed by standardized behavioural scales. Furthermore, we expected a particularly strong link between the level of consciousness and connectivity in the precuneus, reported to be a central node in the DMN (Fransson and Marrelec, 2008), and potentially the most connected area in the brain (Hagmann *et al*., 2008).

Methods

Patients

We compared 14 brain-injured patients (1 locked-in syndrome, 4 minimally conscious, 4 vegetative state and 5 coma patients, age range 25–77 years) to 14 age-matched healthy volunteers (age range 28–57 years). In patients, clinical examination was repeatedly performed using standardized scales [the Coma Recovery Scale-Revised (CRS-R) (Giacino *et al*., 2004); and the Glasgow Liege scale (Born, 1988)] on the day of scanning, and in the week before and the week after. Table 1 reports demographic and clinical characteristics of the patients. Patients were scanned in an unsedated condition. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate to the study was obtained from the subjects themselves in the case of healthy subjects, and from the legal surrogate of the patients.

Data acquisition and analysis

In all subjects, 10 min resting state fMRI were acquired on a 1.5 T magnetic resonance scanner (Siemens, Germany). Two hundred multislice T_2^*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation (36 slices; voxel size: $3.75 \times 3.75 \times 3.6\,\text{mm}^3$; matrix size $64 \times 64 \times 36$; repetition time = 3000 ms; echo time = 30 ms; flip angle = 90°; field of view = 240 mm). Head movements were minimized using customized cushions. A T_1 magnetization prepared rapid gradient echo sequence was also acquired in the same session for coregistration with functional data. Monitoring of vital parameters (electrocardiogram, blood pressure, pulse oxymetry, end tidal carbon dioxide partial pressure and respiratory rate) was performed in patients by a senior anaesthesiologist throughout the experiment.

Data analysis was performed using Statistical Parametric Mapping-5 (www.fil.ion.ucl.ac.uk/spm) and probabilistic independent component analysis (Beckmann and Smith, 2004) as implemented in MELODIC, part of the Functional MRI of the Brain software library (FSL) (www.fmrib.ox.ac.uk/fsl). Independent component analysis is a statistical technique that separates a set of signals into independent (uncorrelated and non-Gaussian) spatio-temporal components (Beckmann and Smith, 2004). When applied to the T_2^* signal of fMRI, independent component analysis allows not only for the removal of artefacts (McKeown *et al*., 1998; Quigley *et al*., 2002), but also for the isolation of task-activated neural networks (McKeown *et al*., 1998; Calhoun *et al*., 2002), or of low-frequency neural networks during task-free or cognitively undemanding fMRI scans (Greicius *et al*., 2004; Beckmann *et al*., 2005; Seeley *et al*., 2007). In a first step, functional images were re-aligned, normalized and smoothed (4 mm full width at half maximum Gaussian kernel) using Statistical Parametric Mapping-5. Independent component analysis was then performed separately for each individual scanning session (one single session was acquired per subject), after removal of low-frequency drifts (150 s high-pass filter). We allowed FSL to use a probabilistic estimation of the number of components as implemented in the probabilistic independent component analysis MELODIC framework (Beckman *et al*., 2005; Beckman and Smith, 2005) aiming to identify the number of non-Gaussian sources in the data (and thus the optimal number of components needed to decompose the data), and attempting to avoid under- or over-fitting due to an incorrect number of sources. The best-fit component for each subject was then selected in an automated three-step process described as the 'goodness-of-fit' approach (Greicius *et al*., 2004, 2008; Seeley *et al*., 2007). This method allows for the unbiased selection of the component for each subject that best corresponds to the DMN. The template used in the present analysis for component selection was obtained from an independent dataset encompassing 19 healthy volunteers (age range 21–31 years) studied on another 3 T MRI scanner (see Supplementary Material for methodological details). First, because intrinsic connectivity is detected in the very low-frequency range (Cordes *et al*., 2001), a frequency filter was applied to remove any components in which high-frequency signal (>0.1 Hz) constituted 50% or more of the power in the Fourier spectrum. Next, we obtained goodness-of-fit scores to the DMN template for the remaining low-frequency components of each subject. To do this, the template-matching procedure calculated the average *Z*-score of voxels falling within the chosen template minus the average *Z*-score of voxels outside the template and selected the component in which this difference (the goodness-of-fit) is the greatest. *Z*-scores here reflect the degree to which the time series of a given voxel correlates with the time series corresponding to the specific independent component analysis component, scaled by the standard deviation of the error term. The *Z*-score is therefore a measure of how many standard deviations the signal is from the background noise. Finally, the component with the highest goodness-of-fit score was selected as the 'best-fit' component and used in the subsequent group analysis. This template-matching procedure was performed separately for each subject. It is important to note that this approach does not alter the components to fit the template in any way, but merely scores the pre-estimated components on how well they match the template (Seeley *et al*., 2007).

Next, all group analyses were performed on the subjects' best-fit component *Z*-score images. We used a random-effects model, estimating the error variance across subjects (Holmes and Friston, 1998), consisting of an ANOVA with the four different states of consciousness (controls, minimally conscious state, vegetative state and coma patients) as the between subjects factor. A correction for non-sphericity was applied to account for potentially unequal variance across groups. A first analysis aimed at identifying the DMN in the control population. A second analysis searched for linear:

$$\left[y = -x - \frac{1}{4}\sum_{i=0}^{3}(-i) \quad x = 0,\ldots,3 \right]$$

non-linear (exponential):

$$\left[y = e^{-x} - \frac{1}{4}\sum_{i=0}^{3} e^{-i} \right]$$

and power law:

$$\left[y = (x+1)^{-1} - \frac{1}{4}\sum_{i=0}^{3}(i+1)^{-1} \right]$$

correlations between DMN connectivity and the level of consciousness (i.e. controls, minimally conscious state, vegetative state and coma). A third analysis looked for differences in DMN connectivity between minimally conscious state and unconscious (vegetative state and coma) patients, using a conjunction approach. A fourth analysis searched for a correlation between DMN connectivity and summed CRS-R scores. A supplementary multiple regression random effects analysis compared the single locked-in syndrome patient to other patient populations. In all our group level analyses, the subjects' age was added as a confounding factor. Results in controls were thresholded at $P < 0.05$ corrected for false discovery rate at the whole brain level. All other analyses were thresholded at $P < 0.05$

Table 1 Clinical, electrophysiological and structural imaging data of patients

	VS1	VS2	VS3	VS4	MCS1	MCS2	MCS3	MCS4	LIS
Clinical Features									
Sex (age, years)	Male (25)	Male (69)	Female (57)	Male (75)	Male (26)	Female (76)	Female (76)	Male (71)	Female (46)
Cause	Trauma	CRA	Haemorrhage	Encephalitis	Trauma	CO intoxication	Stroke	Encephalitis	Stroke
Time of fMRI (days after insult)	159	36	23	69	5 years	16	34	38	16
Outcome at 12 months	GOS 2	GOS 1	GOS 3	GOS 1	GOS 3	GOS 3	GOS 3	GOS 1	GOS 1
Breathing	Spontaneous	Spontaneous—with tube	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Paralysis/paresis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Tetrapraesis	Tetraparesis	Tetraplegia Preserved vertical occulomotricity
CRS-R									
Diagnosis at time of fMRI	VS	VS	VS	VS	MCS	MCS	MCS	MCS	LIS
Auditory function	Startle reflex	None	Startle reflex	Startle reflex	Reproducible movement to command	Startle reflex	Startle reflex	Startle reflex	Consistent movement to command
Visual function	None	None	Blink to threat	None	Visual pursuit	Visual fixation	Visual pursuit	Visual pursuit	Object recognition
Motor function	Flexion to pain	None	None	Flexion to pain	Flexion to pain	None	Automatic motor response	Flexion to pain	Flexion to pain
Oromotor/Verbal function	Oral reflexes	Oral reflexes	Oral reflexes	None	Oral reflexes	Oral reflexes	Oral reflexes	Oral reflexes	Oral reflexes
Communication	None	None	None	None	None	None	None	None	Functional/accurate
Arousal	With stimulation	With stimulation	With stimulation	Without stimulation	Without stimulation	With stimulation	Without stimulation	Without stimulation	Attention
Total score	5	2	4	4	11	5	12	9	16
EEG									
Background activity	Bilateral very slow delta and intermittent theta	Theta with intermittent diffuse delta	Delta-theta irregular	Diffuse delta activity	Low voltage theta, muscular artefacts	Symmetric theta–delta activity	Delta–theta, predominantly on the right side	Theta activity	Theta – with signs of reticular formation impairment
MRI									
Increased intensity on T_2	Diffuse axonal injury (thalamus, mesencephalon, bilateral grey matter)	Bilateral sylvian and frontal lesions	Bilateral frontoparietal lesions	Centro-protuberantial and bilateral white matter lesions	Diffuse leucoencephalopathy and cerebral atrophy Subcortical lesions in basal ganglia and thalamus	Bilateral pallidal lesions	Right frontotemporal lesion	Cerebellar peduncles lesions	Bulbo-medullar junction and cerebellar pedoncules lesions

(continued)

Table 1 Continued

	COMA1	COMA2	COMA3	COMA4	COMA5
Clinical Features					
Sex (age, years)	Female (49)	Male (34)	Male (40)	Male (48)	Female (77)
Cause	Meningioma coma post-surgery	Anoxia	CRA	Haemorrhage	Stroke
Time of fMRI (days after admission)	14	7	7	5	13
Outcome at 12 months	GOS 1	GOS 4	GOS 1	GOS 1	GOS 1
Breathing	Spontaneous	Spontaneous	Spontaneous with tube	Spontaneous	Spontaneous with tube
Paralysis/paresis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis
CRS-R					
Diagnosis at time of fMRI	Coma	Coma	Coma	Coma	Coma
Auditory function	None	None	None	None	Startle reflex
Visual function	None	Blink to threat	None	None	None
Motor function	Abnormal posturing	Flexion to pain	Abnormal posturing	None	Flexion to pain
Oromotor/Verbal function	None	None	None	None	Oral reflexes
Communication	None	None	None	None	None
Arousal	None	None	None	None	None
Total score	1	3	1	0	4
EEG					
Background activity	Theta–delta bilateral	Intermittent theta – delta Abundant spike-wakes and spikes	Generalized status epilepticus	Bilateral posterior theta	Generalized status epilepticus
MRI					
Increased intensity on T_2	Petroclival tumour with cavernous sinus and bulbomedullar junction invasion	None	Diffuse cortical, basal basal ganglia oedema and right capsulo-thalamic lesions	Left temporo-occipital and cerebral peduncles, tegmentum and vermis lesions	Left pulvinar and ascending reticular formation

GOS = Glasgow Outcome Scale; LIS = locked-in syndrome; MCS = minimally conscious state; VS = vegetative state.

corrected for false discovery rate in a 10 mm radius spherical small volume centred on *a priori* coordinates (all peak voxels from an independent DMN connectivity analysis in healthy controls previously published in Boly *et al.*, 2009).

Finally, we computed the power spectrum of the time course of each DMN component and compared obtained peak frequencies (i.e. the frequency with maximum power). Two-tailed permutation tests (Nichols and Holmes, 2002) looked for group differences using EEGLAB (Delorme and Makeig, 2004) implemented in MATLAB 7 (Mathworks, Natick, MA, USA) and results were thresholded for significance at $P < 0.05$.

Results

In controls, the DMN could be reproducibly identified as a set of areas encompassing posterior cingulate cortex (PCC) /precuneus, temporo-parietal junction, medial prefrontal cortex, parahippocampal gyri, superior frontal sulci and thalamus (Fig. 1 and Table 2). The assessed non-linear functions showed a significant correlation between DMN connectivity strength and the level of consciousness in all the previously mentioned areas. Quasi identical results were obtained when exponential or power law contrasts were employed, whereas a less good fit was observed for the linear correlation, though linear correlation between connectivity and consciousness was significant (Table 3 and Fig. 2 show results for the exponential correlation). Clinical experience indicates that the decrease in consciousness between normal wakefulness, minimally conscious, vegetative state and coma is indeed non-linear (vegetative state patients' consciousness being closer to comatose patients' consciousness than to minimal consciousness). In all analyses, the peak area of significance for the correlation between connectivity and consciousness was found to be the PCC/precuneus. PCC/precuneus connectivity was also found to differentiate minimally conscious from unconscious patients (Table 4, Fig. 3). No brain area was found to be more present in DMN connectivity maps in unconscious compared with minimally conscious patients. No brain area could be identified as presenting a weaker connectivity in the single locked-in syndrome patient compared with controls. For illustrative purposes, the locked-in syndrome patient's data are displayed as red circles in Fig. 2, allowing comparison to controls' and patients' data.

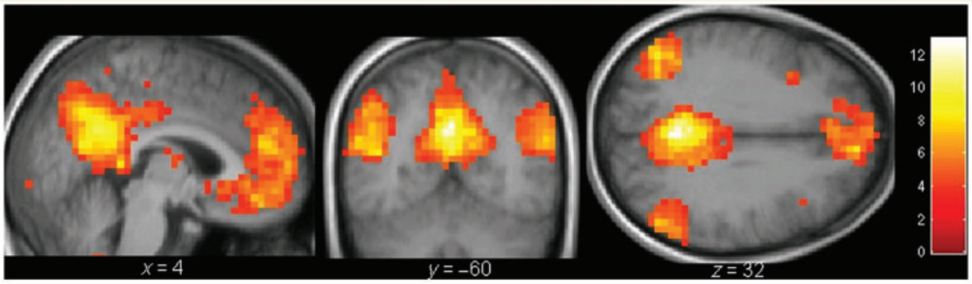


Figure 1 Default network identified in controls. Results are thresholded for display at whole brain false discovery rate corrected $P < 0.01$ and rendered on the mean T_1 structural image of the controls.

Table 2 Peak voxels of the default network identified in healthy volunteers

Areas		x	y	z	Z-value	P-value
Posterior cingulate cortex/precuneus		−8	−52	28	6.82	<0.001
Medial prefrontal cortex		8	52	32	5.53	<0.001
Superior frontal sulcus	R	28	24	40	5.22	<0.001
	L	−20	36	48	6.05	<0.001
Temporo-parietal junction	R	52	−56	24	5.41	<0.001
	L	−48	−56	20	5.92	<0.001
Parahippocampal gyrus	L	−28	−32	−20	4.95	<0.001
Temporal cortex	R	64	−8	−24	5.44	<0.001
	L	−60	−12	−24	4.82	<0.001
Inferior frontal gyrus	R	40	24	−20	4.04	0.001
Post-central gyrus	L	−52	−16	44	3.59	0.002
Insula	L	−32	−16	8	3.00	0.013
Thalamus		−8	−8	0	2.73	0.025
Brainstem		0	−20	−24	2.71	0.026
Cerebellum	R	12	−44	−40	3.55	0.003
	L	−28	−80	−36	4.75	<0.001

P-values are corrected for false discovery rate at the whole brain level.

Table 3 Peak voxels showing an exponential correlation between default network connectivity and the level of consciousness

Areas		x	y	z	Z-value	P-value
Posterior cingulate cortex/precuneus		−8	−52	28	4.89	0.004
Medial prefrontal cortex		0	52	−20	3.52	0.025
Superior frontal sulcus	R	8	52	35	4.62	0.005
	L	−20	36	48	4.66	0.004
Temporo-parietal junction	R	60	−64	24	3.56	0.025
	L	−48	−68	24	4.10	0.009
Parahippocampal gyrus	L	−32	−20	−24	3.83	0.014
Temporal cortex	R	56	−12	−24	4.29	0.007
	L	−48	−56	20	4.26	0.007
Precentral gyrus	L	−48	−20	52	3.83	0.014
Postcentral gyrus	L	−52	−16	44	3.35	0.033
Thalamus		−24	−24	12	4.17	0.008
		8	−12	12	3.32	0.034
Brainstem		4	−24	−36	3.31	0.035
Cerebellum	R	12	−44	−40	3.90	0.012
	L	−28	−80	−36	3.46	0.028

P-values are corrected for false discovery rate for whole brain.

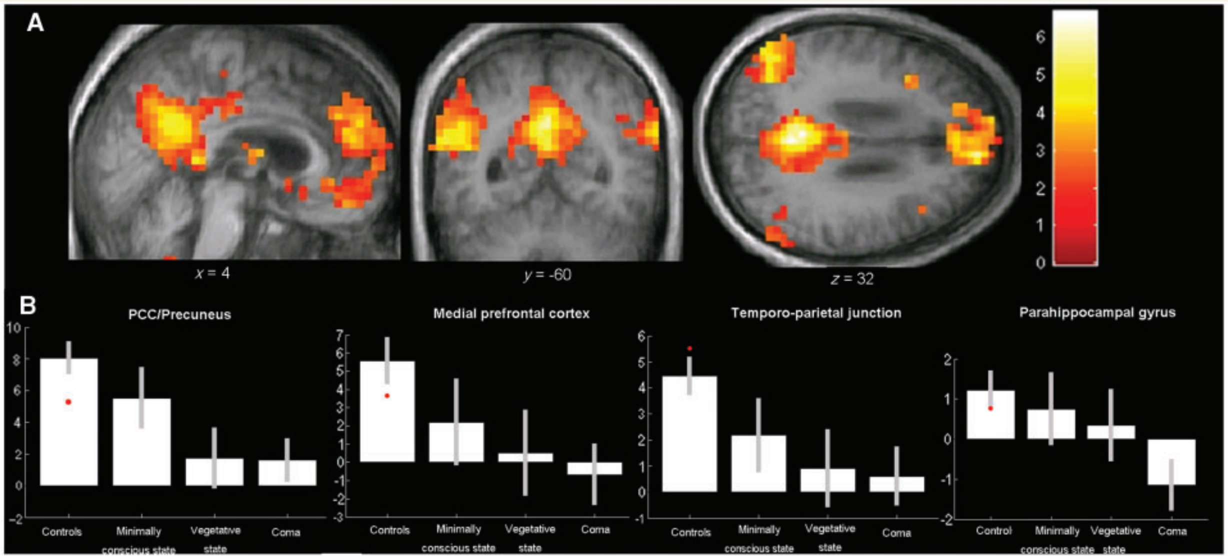


Figure 2 Default network connectivity correlates with the level of consciousness, ranging from healthy controls, to minimally conscious, vegetative then comatose patients. (**A**) Areas showing a linear correlation between default network connectivity and consciousness. Results are thresholded for display at uncorrected $P < 0.05$ and rendered on the mean T_1 structural image of the patients. (**B**) Mean *Z*-scores and 90% confidence interval for default network connectivity in PCC/precuneus, temporo-parietal junction, medial prefrontal cortex and parahippocampal gyrus across patient populations. Locked-in syndrome patient *Z*-scores are displayed for illustrative purposes as an additional red circles overlaid on control population data.

We observed a correlation between connectivity and CRS-R total scores in most of the DMN (Table 5), but results only survived correction for multiple comparisons in the medial prefrontal gyrus.

The total number of components and the proportion of variance explained by the DMN component were not significantly different in patients as compared with healthy controls [33 ± 20 (range 11–68) versus 27 ± 4 (range 21–35) components; and 4.1 ± 2.3 (range 1.2–8.7) versus 3.6 ± 0.8 (range 2.6–5.7), respectively]. Finally, the power spectrum of the DMN time courses showed a non-significant increase in peak frequency in patients as compared with healthy volunteers (mean ± SD, 0.040 ± 0.037 range 0.001–0.100 Hz versus 0.020 ± 0.013 range 0.001–0.056 Hz, respectively).

Table 4 **Default network areas differentiating minimally conscious from unconscious (vegetative and coma) patients (conjunction approach)**

Areas		x	y	z	Z-value	P-value
Minimally conscious state > unconscious						
Posterior cingulate cortex/precuneus		20	−48	32	3.62	0.012
Medial prefrontal cortex		−4	52	−24	1.81	0.035*
Temporo-parietal junction	R	64	−52	24	2.35	0.010*
Parahippocampal cortex	L	−32	−20	−24	2.11	0.017*
Temporal cortex	R	60	−56	28	2.35	0.010*
Thalamus		−24	−28	−12	1.75	0.040*
Brainstem		12	−16	−16	1.70	0.045*
Minimally conscious state < unconscious						
No areas could be identified						

P-values are corrected for false discovery rate in a 10 mm radius spherical small volume centred on *a priori* coordinates. *Non-corrected *P*-values.

Figure 3 Brain areas within the default network connectivity which differentiate minimally conscious patients from unconscious patients. Results are thresholded for display at uncorrected $P < 0.05$ and rendered on the mean T_1 structural image of the patients.

Table 5 **Peak voxels showing a correlation between default network connectivity and the CRS-R total score**

Areas		x	y	z	Z-value	P-value
Posterior cingulate cortex/precuneus		8	−32	40	2.34	0.010*
Medial frontal gyrus		−4	48	36	3.78	0.006
Superior frontal sulcus	R	16	32	40	1.70	0.044*
Parahippocampal cortex	L	−40	−4	−24	1.86	0.032*
Temporo-parietal junction	R	44	−68	48	1.89	0.030*
	L	−40	−64	52	2.07	0.019*
Temporal cortex	R	60	0	40	2.36	0.009*
	L	−60	−8	−28	1.99	0.023*
Thalamus		−16	−36	8	2.10	0.018*
Brainstem		−4	−28	−48	2.30	0.011*

P-values are corrected for false discovery rate in a 10 mm radius spherical small volume centred on *a priori* coordinates. *Non-corrected *P*-values.

Discussion

Clinical and neuroscientific relevance of a correlation between DMN connectivity and the level of consciousness

Using resting state fMRI connectivity analyses, we showed an exponential correlation between DMN connectivity integrity and the level of consciousness of brain-damaged patients ranging from controls, to minimally conscious, vegetative state then coma patients. These results suggest that, although the DMN can still be identified in unconscious patients, as in anaesthetized monkeys (Vincent *et al.*, 2007), connectivity strength within DMN could possibly be a reliable indicator of a patient's level of consciousness, differentiating unconscious patients such as those in a coma or vegetative state from minimally conscious and locked-in syndrome patients. As resting state fMRI studies are much easier to acquire in a routine clinical setting than standard fMRI paradigms, these connectivity studies could potentially be a useful complement to bedside behavioural assessment in the evaluation of the level of consciousness of non-communicative brain-damaged patients. Note that CRS-R total scores showed a less significant fit as compared with the non-linear correlation with DMN connectivity. In our view, this is explained by the fact that the CRS-R total score was not developed to differentiate between different levels of consciousness (e.g. a minimally conscious patient may have an identical CRS-R total score as a vegetative state patient).

In addition to its potential clinical relevance, the finding that DMN connectivity strength is proportional to the level of consciousness of brain-damaged patients sheds light on the significance of spontaneous brain activity fluctuations as recorded by fMRI. Our results suggest that the strength of connectivity in resting state fMRI-identified networks could be related in a quantitative manner to the level of conscious processing in severely brain-damaged patients. These results complement previous findings showing partially preserved connectivity in states of altered consciousness like vegetative state (Boly *et al.*, 2009), light sleep (Horovitz *et al.*, 2008) or anaesthetized monkey (Vincent *et al.*, 2007). Our results are also in line with recent reports of decreased DMN connectivity in healthy volunteers during sedation (Greicius *et al.*, 2008) and deep sleep (Horovitz *et al.*, 2009). Larson-Prior *et al.* (2009), however, observed no measurable change in DMN connectivity during light sleep. Taken together, these findings suggest a two-layer view of resting state fMRI DMN connectivity: one part of the DMN connectivity would persist independently of the level of consciousness, and possibly related to underlying anatomical connectivity (Vincent *et al.,* 2007; Greicius *et al.*, 2009), and the other part being more tightly related to the presence of conscious cognitive processes. More generally, the finding of decreased DMN connectivity in proportion to impairment of consciousness is consistent with previous findings of metabolic impairment of a large frontoparietal network, encompassing main nodes of the DMN, in patients in vegetative state compared with controls, as well as in other states of clinical unconsciousness such as sleep, anaesthesia, seizures or somnambulism (Baars *et al.*, 2003; Laureys, 2005). The current results are also consistent with the so-called ‘global workspace’ theory of consciousness (Baars *et al.*, 2003; Dehaene and Changeux, 2005), by suggesting that higher order frontoparietal areas are likely to play a crucial role in the genesis of conscious perception. However, we should remain cautious when interpreting the functional significance of DMN connectivity measurements in terms of consciousness. More investigations on physiological (e.g. sleep and hypnotic state), pharmacological (e.g. general anaesthesia) and pathological alterations of consciousness in health and disease subjects, are awaited before a consensus can be reached on the precise functional meaning of this network.

The maximum peak of significance for a correlation between DMN connectivity and consciousness was found in the PCC/precuneus. This finding is coherent with studies showing a central role of precuneus in DMN architecture, from the functional (Fransson and Marrelec, 2008) to the structural point of view (Hagmann *et al.*, 2008). Precuneus connectivity could also reliably differentiate minimally conscious from unconscious patients, again suggesting a particularly strong relationship between the level of activity of this area and the patients’ level of consciousness (Laureys *et al.*, 2004; Cavanna and Trimble, 2006). As the DMN has been suggested to be involved in ‘mind-wandering’ (Mason *et al.*, 2007) and self-referential processes (Cavanna and Trimble, 2006; Cavanna, 2007), our results could also imply that minimally conscious patients have a partially preserved level of self-awareness or ‘day-dreaming’-like cognition or, at a minimum, have the residual functional architecture to support such complex processes. This finding stresses the importance of assessing residual cognitive functions in patients with disorders of consciousness, which could be largely underestimated at the clinical bedside.

It should be noted that while the thalamus has not been reported in all DMN connectivity studies in the literature, it has been described in papers on healthy volunteers in recent years (Fransson, 2005; De Luca *et al*., 2006; Greicius *et al.,* 2007; Boly *et al*., 2009). Thalamo-cortical loops have been increasingly associated with conscious perception (Laureys *et al*., 2000; White and Alkire, 2003; Schiff *et al.*, 2007), possibly explaining our observed correlation between consciousness and thalamo-cortical DMN connectivity.

Technical issues in the study of resting state fMRI connectivity in severely brain-damaged patients

Several technical issues should be discussed in the study of connectivity in patients with altered states of consciousness. While the acquisition of resting state fMRI data is easier than standard fMRI paradigms, spontaneous blood oxygen level dependent fluctuations measures are subject to more artefactual bias than evoked data (Morcom and Fletcher, 2007). Therefore, resting state fMRI analyses should include a method for carefully separating relevant signal from artefacts present in the data. Independent component analysis is especially suited to this aim. Compared with region of interest-driven correlation analyses, independent component analysis offers the double advantage of being able to isolate cortical connectivity maps from non-neural signals (Beckmann *et al*., 2005; Beckman and Smith, 2005; Seeley *et al.*, 2007), and of being unbiased by the selection of a seed region-of-interest for correlation analysis. Therefore, independent component analysis may allow the identification of network nodes missed by the conventional region of interest-driven analysis (Seeley *et al*., 2007). The selection of relevant components of interest is still an issue when dealing with the outputs of independent component analysis. In a clinical framework, the use of an automated component selection approach, as used in the present analysis, is ideally required, in order to avoid subjective bias in the interpretation of data. In this study, the template used for automatic DMN component selection was issued from an independent connectivity study on a separate group of healthy volunteers, and was applied to both controls and patients. It should be noted that this methodology, classically employed in clinical studies on DMN connectivity [e.g. in dementia (Greicius *et al*., 2004), depression (Greicius *et al.*, 2007) or epileptic patients (Zhang *et al.*, 2009)], might bias the selection towards the healthy control group. Future work should compare the presently used ‘goodness-of-fit’ approach to other component selection approaches based on spatial similarity with templates, or ‘fingerprinting’ approaches [i.e. graphical representations of independent components in multidimensional space encompassing spatial and temporal entropy, kurtosis, one-lag auto-correlation and power contributions in different frequency bands (De Martino *et al.*, 2007)] in order to test for reliability at the individual level. Another remaining question is the relationship between structural and functional connectivity changes in non-communicative brain-damaged patients. Functional connectivity in DMN has indeed been related to underlying structural anatomy (Greicius *et al.*, 2009). Further multimodal studies should combine resting state functional MRI data with structural MRI (e.g. diffusion tensor imaging data) or high-density EEG recordings.

Conclusion

We here identified a significant correlation, at the group-level, between DMN connectivity and the level of consciousness. These results suggest that after further validation, the present methodology could potentially be rapidly translated into a routine clinical setting and bring relevant ancillary information on a patient’s residual brain function to bear on their clinical evaluation. The presence of an exponential correlation between DMN connectivity and consciousness suggests that resting state fMRI could be a potentially useful paraclinical marker of the level of consciousness in non-communicative brain-damaged patients, complementing their bedside assessment. Future studies on larger samples of patients will aim at correlating resting state fMRI connectivity with prognosis and white matter damage (as assessed, for example, by diffusion tensor imaging) in individual brain-damaged patients.

Acknowledgements

The authors thank the technicians of the Department of Neuro-Radiology and the nurses of the Intensive Care and Neurology Departments of the Centre Hospitalier Universitaire of Liège for their active participation in the MRI studies in comatose patients. M.-A.B. is Research Fellow, M.B., Q.N. and C.S. are Post-doctoral Fellows, and S.L. and P.M. are Senior Research Associates at the FNRS, AV is Research Fellow at the ARC 06/11-340.

Funding

Belgian Fonds National de la Recherche Scientifique (FNRS); European Commission (Mindbridge, DISCOS, CATIA and DECODER); Mind Science Foundation; James McDonnell Foundation; French Speaking Community Concerted Research Action (ARC 06/11-340); Fondation Médicale Reine Elisabeth; NIH (NS048302 to MD.G.).

Supplementary material

Supplementary material is available at *Brain* online.

References

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: 205–9.

Baars BJ, Ramsoy TZ, Laureys S. Brain, conscious experience and the observing self. Trends Neurosci 2003; 26: 671–5.

Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 2005; 360: 1001–13.

Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 2004; 23: 137–52.

Beckmann CF, Smith SM. Tensorial extensions of independent component analysis for multisubject FMRI analysis. Neuroimage 2005; 25: 294–311.

Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas P, Del Fiore G, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 2004; 61: 233–8.

Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol 2008a; 7: 1013–20.

Boly M, Phillips C, Tshibanda L, Vanhaudenhuyse A, Schabus M, Dang-Vu TT, et al. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Ann N Y Acad Sci 2008b; 1129: 119–29.

Boly M, Tshibanda L, Noirhomme Q, Vanhaudenhuyse A, Schnakers C, Ledoux D, et al. 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: 2393–400.

Born JD. The Glasgow–Liège Scale Prognostic value and evaluation of motor response and brain stem reflexes after severe head injury. Acta Neurochir 1988; 91: 9549–52.

Buckner RL, Andrews-Hanna JR, Schacter DL. The brain’s default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008; 1124: 1–38.

Calhoun VD, Pekar JJ, McGinty VB, Adali T, Watson TD, Pearlson GD. Different activation dynamics in multiple neural systems during simulated driving. Hum Brain Mapp 2002; 16: 158–67.

Cavanna AE. The precuneus and consciousness. CNS Spectr 2007; 12: 545–52.

Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129 (Pt 3): 564–83.

Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 2001; 22: 1326–33.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 2006; 103: 13848–53.

Dehaene S, Changeux JP. Ongoing spontaneous activity controls access to consciousness: a neuronal model for inattentional blindness. PLoS Biol 2005; 3: e141.

Delorme A, Makeig S. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004; 134: 9–21.

De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 2006; 29: 1359–67.

De Martino F, Gentile F, Esposito F, Balsi M, Di Salle, Goebel FR, et al. Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. Neuroimage 2007; 34: 177–94.

Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 2005; 26: 15–29.

Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. Neuroimage 2008; 42: 1178–84.

Giacino JT. The minimally conscious state: defining the borders of consciousness. Prog Brain Res 2005; 150: 381–95.

Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002; 58: 349–53.

Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004; 85: 2020–9.

Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 2007; 62: 429–37.

Greicius MD, Kiviniemi V, Tervonen O, Vainionpaa V, Alahuhta S, Reiss AL, et al. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp 2008; 29: 839–47.

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 2004; 101: 4637–42.

Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 2009; 19: 72–8.

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the structural core of human cerebral cortex. PLoS Biol 2008; 6: 159.

Holmes A, Friston K. Generalisability, random effects and population inference. Neuroimage 1998; 7: 754.

Horovitz SG, Braunc AR, Carrd WS, Picchionie D, Balkine TJ, Fukunagab M, et al. Decoupling of the brain's default mode network during deep sleep. Proc Natl Acad Sci USA 2009; 106: 11376–81.

Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, et al. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. Hum Brain Mapp 2008; 29: 671–82.

Larson-Prior LJ, Zempel JM, Nolana TS, Prior FW, Snyder AZ, Raichle MA. Cortical network functional connectivity in the descent to sleep. Proc Natl Acad Sci USA 2009; 106: 4489–94.

Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci 2005; 9: 556–9.

Laureys S, Boly M. What is it like to be vegetative or minimally conscious? Curr Opin Neurol 2007; 20: 609–13.

Laureys S, Boly M. The changing spectrum of coma. Nat Clin Pract Neurol 2008; 4: 544–6.

Laureys S, Faymonville ME, Moonen G, Luxen A, Maquet P. PET scanning and neuronal loss in acute vegetative state. Lancet 2000; 355: 1825–6.

Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004; 3: 537–46.

Laureys S, Perrin F, Bredart S. Self-consciousness in non-communicative patients. Conscious Cogn 2007; 16: 722–41; discussion 742–25.

Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. Prog Brain Res 2005; 150: 397–413.

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. Science 2007; 315: 393–5.

McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, et al. Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp 1998; 6: 160–88.

Morcom AM, Fletcher PC. Does the brain have a baseline? Why we should be resisting a rest. Neuroimage 2007; 37:1073–82.

Nichols T, Holmes A. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002; 15: 1–25.

Quigley MA, Haughton VM, Carew J, Cordes D, Moritz CH, Meyerand ME. Comparison of independent component analysis and conventional hypothesis-driven analysis for clinical functional MR image processing. AJNR Am J Neuroradiol 2002; 23: 49–58.

Raichle ME. Neuroscience. The brain's dark energy. Science 2006; 314: 1249–50.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001; 98: 676–82.

Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007; 448: 600–3.

Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurology 2009; 9: 35.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007; 27: 2349–56.

Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, et al. The resting brain: unconstrained yet reliable. Cereb Cortex 2009; 19: 2209–29.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, et al. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 2007; 447: 83–6.

White NS, Alkire MT. Impaired thalamocortical connectivity in humans during general-anesthetic-induced unconsciousness. Neuroimage 2003; 19 (2 Pt 1): 402–11.

Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Chen Z, et al. Impaired perceptual networks in temporal lobe epilepsy revealed by resting fMRI. J Neurol 2009; 256: 1705–13.

TWO DISTINCT NEURONAL NETWORKS MEDIATE THE AWARENESS OF ENVIRONMENT AND OF SELF

Audrey Vanhaudenhuyse[1]†, Athena Demertzi[1]†, Manuel Schabus[3], Noirhomme Quentin[1], Serge Bredart[2], Melanie Boly[1], Christophe Phillips[1], Andrea Soddu[1], Andre Luxen[1], Gustave Moonen[1], Steven Laureys[1]

[1] Coma Science Group, Cyclotron Research Center, University of Liège, Allée du 6 août 8 , Sart Tilman B30 – 4000, Liège, Belgium.

[2] Cognitive Psychology Unit, Department of Cognitive Sciences, University of Liège, Bd. du Rectorat 5, Sart Tilman B32- 4000 Liège, Belgium.

[3] Department of Psychology, Division of Physiological Psychology, University of Salzburg, Hellbrunnerstrasse 34, 5020, Salzburg, Austria.

†A.V. and A.D. contributed equally to this work.

Corresponding author:

Pr . Steven Laureys

Cyclotron Research Center

Sart Tilman-B30

4000 Liège, Belgique

Tel: +32 4 366 23 16

Fax: +32 4 366 29 46

Email: steven.laureys@ulg.ac.be

For Review Only

ABSTRACT

Evidence from functional neuroimaging studies on resting state suggests that there are two distinct anticorrelated cortical systems that mediate conscious awareness: an ‘extrinsic’ system that encompasses lateral fronto-parietal areas and which has been linked with processes of external input (external awareness) and an ‘intrinsic’ system which encompasses mainly medial brain areas and which have been associated with internal processes (internal awareness). The aim of our study was to explore the neural correlates of resting state by providing behavioral and neuroimaging data from healthy volunteers. With no a priori assumptions, we first determined behaviorally the relationship between external and internal awareness in 31 subjects. We found a significant anticorrelation between external and internal awareness with mean switching frequency of 0.05 Hz (range: 0.01-0.1Hz). Interestingly, this frequency is similar to BOLD fMRI slow oscillations. We then evaluated 22 healthy volunteers in a fMRI paradigm looking for brain areas where BOLD activity correlated with ‘internal’ and ‘external’ scores. Activation of precuneus/posterior cingulate, anterior cingulate/mesiofrontal cortices and parahippocampal areas (‘intrinsic system’) was linearly linked to intensity of internal awareness whereas activation of lateral fronto-parietal cortices (‘extrinsic system’) was linearly associated with intensity of external awareness.

For Review Only

INTRODUCTION

Consciousness has two components, arousal and awareness (Zeman, 2001). Arousal refers to the levels of alertness or vigilance and involves the activity of brainstem reticular formation, hypothalamus and basal forebrain; while awareness refers to the contents of consciousness and is related to the activity of a widespread set of frontoparietal associative areas. Awareness and arousal are linearly correlated, in the sense that the less aroused we get the less aware of our surroundings and ourselves we become (Laureys, 2005). Furthermore, awareness encompasses two components: awareness of the environment (external) and of self (internal) (James, 1890). We here define external awareness as the conscious perception of one's environment through the sensory modalities (e.g., visual, auditory, somesthetic or olfactory perception). Internal awareness is defined as encompassing mental processes that do not require the mediation of external stimuli or sensory input (e.g., mind wandering, daydreaming, inner speech, mental imagery; for review see Lieberman, 2007). Growing neuroscientific evidence supports that the awareness brain network can be subdivided in two main networks: a frontoparietal network routinely exhibiting activity increases during attention-demanding cognitive tasks, and a "default network" which has been involved in self-related processes (Fox et al., 2005).

For Review Only

The aim of the present study is to better characterize the subjective cognitive processes inherent to these "external" and "internal" or "default" networks. We first performed a behavioral experiment looking for the relationship between subjective external and internal awareness scores in 31 healthy volunteers. During an eyes-closed resting condition, subjects were asked to score their external and internal awareness levels by button-presses after hearing an auditory prompt. Next, we performed a functional magnetic resonance imaging (fMRI) experiment in 22 subjects looking for the neural correlates of subjective external and internal awareness scores, correlating “external” and “internal” awareness intensity to changes in BOLD (blood oxygen level dependent) neural activity.

MATERIAL AND METHODS

Before each experiment, subjects received the following instruction: “During the next 15 minutes, we ask you to keep the eyes closed and to avoid prolonged structured thinking, such as counting or singing. When you hear a beep, please use the keyboard to communicate the intensity of ‘external awareness’ and ‘internal awareness’ ongoing prior to the beep. ‘External’ is here defined as perception of environmental sensory stimuli (e.g., auditory, visual, olfactory or somesthetic). ‘Internal’ here refers to all environmental stimuli-independent thoughts (e.g., inner speech, autobiographical memories or wandering thoughts).”

Participants

Behavioral data were acquired from 31 healthy subjects (21 women, mean age 26±3 (SD)). Imaging data were acquired from 22 healthy subjects, different from the subjects of the behavioral study (10 women, mean age 23±2 (SD)), one participant was excluded from further analysis due to movement artifacts. None of the participants had any relevant medical history or used any centrally acting medication. All participants gave their written informed consent prior inclusion in the study, which was approved by the Ethics Committee of the University of Liège.

Behavioral experiment

Our experimental exploration consists of two parts. First, a behavioral experiment was used in order to determine the relationship between external and internal awareness. External

For Review Only

and internal awareness scores were recorded using a keyboard. The experiment took place in a quiet room where the subjects were seated comfortably in a chair facing the keyboard used for recording awareness scores. Subjects placed four fingers of both hands (not the thumb) on the keyboard. For the first behavioral study, for the half of the subjects, left hand corresponded to external awareness (for the other half, left hand corresponded to internal awareness; randomized order). All subjects were instructed to start responding by using button presses of their left hand on a four-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = maximal). The subjects' task was to rate both external and internal awareness (prompted by a 60 dB beep presented via headphones), as defined in the instruction mentioned above. Only when the two scores were given, could the next beep be elicited. Inter-stimulus interval was randomized between 11.3-26.8s (mean 19±8s). A familiarization session (11 responses) preceded the main experiment (66 responses). Upon completion of the experiment, the content of external and internal awareness was assessed using a semi-structured interview.

For Review Only

Statistical analysis. The relationship between ratings of external and internal awareness was estimated by calculating the Spearman's r correlation coefficients (two-tailed) for every subject and then estimating the mean correlation within the sample. In terms of temporal dynamics, the frequency of switching between internal and external awareness scores was estimated by first subtracting the external from internal ratings in order to get a unique curve for every subject. The frequency spectrum of these obtained scores was estimated using the Lomb periodogram method for unevenly sampled awareness scores (Lomb, 1976; Press, Flannery, Teukolsky & Vetterling, 1992).

Imaging experiment

After having established the relationship between external and internal awareness with the behavioral experiment (using responses from both hands), the fMRI study was performed. Here, in order to reduce the interference with resting state brain function and to reduce motor responses and artifacts to the maximum, behavioral responses were obtained on a single scale reflecting intensity from 'more external' to 'more internal' awareness. Hence, for the fMRI experiment awareness scores were recorded with the left hand for all subjects (1 = strongly external, 2 = moderately external, 3 = moderately internal and 4 = strongly internal). During the scanning period, subjects were asked not to move, to keep their eyes closed, to relax and to avoid structured thinking (e.g., counting, singing, etc). Subjects were presented an auditory beep on average every 20 seconds (range 3 to 30 s). After each sound, subjects were asked to evaluate and score by a button press their state of awareness (‘strongly external’, ‘moderately external’, ‘moderately internal’ and ‘strongly internal’) for the time period preceding the beep. The fMRI study was terminated when online analysis showed 15 responses in each state of awareness.

Paired student T tests assessed differences in reaction times between external and internal awareness states. Similarly to the behavioral experiment, the frequency spectrum of awareness scores obtained during the fMRI data was estimated using the Lomb method for unevenly sampled data (Lomb, 1976; Press, Flannery, Teukolsky & Vetterling, 1992).

MRI acquisition. Functional MRI time series were acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. Multislice T_2*-weighted functional images were acquired with a gradient-echo planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220x220 mm², voxel size 3.4x3.4x3 mm³, 30%

For Review Only

interslice gap, matrix size 64x64x32, TR = 2460 ms, TE = 40 ms, FA = 90°). The three initial volumes were discarded to avoid T_1 saturation effects. For anatomical reference, a high-resolution T_1-weighted image was acquired for each subject (T_1-weighted 3D magnetization-prepared rapid gradient echo sequence, TR = 1960 ms, TE = 4.43 ms, inversion time (TI) = 1100 ms, FoV = 230x173 mm^2, matrix size = 256x192x176, voxel size = 0.9x0.9x0.9 mm^3).

MRI analysis. Functional data were preprocessed and analyzed by means of Statistical Parametric Mapping software SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/; Wellcome Department of Imaging Neuroscience, London, U.K.), using a two steps procedure (random effect analysis) taking into account bout within and between subject variability as we published elsewhere (Boly et al. 2007; Vanhaudenhuyse et al. 2009; Boly et al. 2007). The first two fMRI volumes were removed to allow for signal equilibration. Preprocessing steps included realignment, spatial normalization, and smoothing (Friston et al., 1995a; 1995b). The normalization was performed using a three-steps automated procedure (Friston et al., 1995a). Firstly, the structural T1 scan of each subject was segmented and normalization parameters were derived from this step from the subject space to the MNI space. Secondly, the functional data were coregistered to the structural scan. Thirdly, the structural and functional scans were normalized using the normalization parameters (voxel size: 2×2×2 mm for functional and 1×1×1 mm for structural images) derived from the first step. Functional data were then smoothed using an 8mm full width at half maximum Gaussian kernel. Each subject's data were modeled individually with a Generalized Linear Model (Friston et al., 1995b) and images of effects of interest were produced. These images were then analyzed with a mixed-effects model aimed at showing stereotypical effect in the population from which the subjects are drawn (Penny & Holmes, 2003). The mixed-effects model was implemented in two

For Review Only

processing steps accounting for fixed and random effects, respectively (Friston et al., 2005; Boly et al., 2007).

For each subject, a first-level intra-individual fixed effects analysis aimed at modeling the data to partition the observed neurophysiological responses into components of interest, confounds, and errors by using a general linear model (Friston et al., 1995b, Boly et al., 2007, Vanhaudenhuyse et al., 2009). We created a design matrix using a block design (lasting 3 to 30 s) for every individual subjects incorporating answers of subjects (‘strongly external’, ‘moderately external’, ‘moderately internal’ and ‘strongly internal’) as regressors of interest, time of beeps, reaction time and movements parameters as supplementary regressors. Reaction times were calculated by subtracting time of answer to time of beep. Movement parameters derived from realignment of the functional volumes (translations in the x, y, and z directions and rotations around the x, y, and z axes). Reaction times and movement parameters were included as covariates of no interest in the design matrix. A first analysis identified stimulus-induced brain activation in periods rated as ‘strongly external’, ‘moderately external’, ‘moderately internal’ and ‘strongly internal’. These periods were incorporated as regressors of interest in the design matrix using a block design (lasting 3 to 30 s). The movements were modeled in supplementary regressors. Movement parameters derived from realignment of the functional volumes (translations in the x, y, and z directions and rotations around the x, y, and z axes) were included as covariates of no interest in the design matrix. High-pass filtering using a cut-off period of 128s was implemented in the design matrix to remove low-frequency drift from the time series (Friston et al., 2000; Boly et al., 2007; Vanhaudenhuyse et al., 2009). Serial correlations were estimated using a restricted maximum likelihood algorithm with an intrinsic autoregressive model during parameter estimation. The effects of interest were tested through linear contrasts, generating statistical parametric maps (SPM t) in each subject. Contrasts images were computed, identifying a

For Review Only

linear positive correlation with external thoughts (1.5 0.5 -0.5 -1.5 contrast of the general linear model parameters) and a linear positive correlation with internal thoughts (contrast -1.5 -0.5 0.5 1.5). The resulting set of voxel values for each contrast constituted a map of t statistic (SPM T) thresholded at $p<0.001$ (Peigneux et al., 2006). We then smoothed the contrast images (6mm FWHM Gaussian kernel) in order to improve statistic across subjects by increasing the overlap between activated areas of each subject, and balancing the existing inter-subject anatomical variability (Mikl et al., 2008; White et al., 2001). These smoothed contrast images were entered in a second-level general linear model, acting as a random effects analysis investigating consistent effects at the population level. Statistical inferences were then obtained after correction for multiple comparison at the voxel level using false discovery rate (FDR) $p<0.05$ (whole head volume) for areas previously reported to be involved in internal awareness (i.e., mesiofrontal/anterior cingulate and precuneal/posterior cingulate cortices, Boly et al., 2007; Mason et al., 2007; Laureys, Perrin & Bredart, 2007) ; while a small volume (8mm radius sphere) corrected at $p<0.05$ (Worsley, 1996) was calculated for areas previously reported to be involved in external awareness (i.e., bilateral posterior parietal and dorsolateral prefrontal cortex, Boly et al., 2007; Dehaene et al., 2001; Haynes, Driver & Rees, 2005; Vuilleumier et al., 2001). , and internal awareness (i.e., mesiofrontal/anterior cingulate and precuneal/posterior cingulate cortices, Boly et al., 2007; Mason et al., 2007; Laureys, Perrin & Bredart, 2007).

For Review Only

RESULTS

Behavioral experiment

We observed a significant negative correlation between external and internal awareness scores at the group level (Spearman's $r = -.44$, $p<.02$, two-tailed). At the subject level, 24 participants showed significant negative correlations between internal and external awareness, one showed a positive correlation and six participants showed non-significant correlations. The switching between external and internal awareness was calculated to occur on average with a mean frequency of 0.05 ± 0.03 Hz (SD) frequency (range= 0.01- 0.1 Hz) (Figure 1). External thoughts reported were auditory in 65% of subjects, somesthetic in 58%, olfactory in 13% and visual in 1%; internal thoughts were experiment-related in 52%, autobiographical in 42% and inner speech in 13% of subjects. The contents of external and internal awareness are summarized in Table 1.

For Review Only

INSERT FIGURE 1

INSERT TABLE 1

fMRI experiment

Scanning was ended when online analysis showed at least 15 responses in each state of awareness (meaning 18±2 minutes (X±SD)). Intensity of internal awareness intensity correlated linearly with activity in posterior cingulate/precuneal, anterior cingulate/mesiofrontal and bilateral parahippocampal cortices (whole-brain FDR<0.05 – Figure 2 – blue areas, Table 2A). Intensity of external awareness scores correlated linearly with activity in bilateral inferior frontal gyrus and inferior parietal lobule (small-volume correction – Figure 2 – red areas, Table 2B). Additional contrasts looking for linear positive correlations with external thoughts only (1.5 0.5 0 0), independently of a linear positive correlation with internal thoughts only (0 0 0.5 1.5) showed similar results.

Reaction times obtained during the fMRI study did not differ when subjects were in "extrinsic" modes as compared to those obtained during "intrinsic" modes of conscious activity (mean (SD) 1352±1132 ms versus 1427±837 ms; t(20)=0,72; p=0.48).The switching between external and internal awareness was calculated (Laguna et al., 1998) to occur with a mean frequency of 0.03±0.004 Hz (SD) frequency (range= 0.03- 0.4 Hz). The mean duration of periods of external (mean 28±41s (SD)) versus internal awareness (29±66s) were not significantly different (p = 0.35).

INSERT FIGURE 2

INSERT TABLE 2

DISCUSSION

Growing neuroscientific evidence supports the idea that the brain's intrinsic or default activity is essential to its global functioning (Raichel & Snyder, 2007). This notion was initially stressed by positron emission tomography (PET) studies, which revealed metabolic decreases in specific brain areas (e.g., posterior cingulate/precuneal and anterior cingulate/medial-prefrontal cortices) during performance of specific cognitive tasks as compared to passive resting state (Shulman et al., 1997). Raichle and colleagues considered these 'deactivations' as deviations from an ongoing metabolic/physiologic baseline which characterizes the functionality not only of the aforementioned areas, the so-called 'default network', but of most areas of the brain (Raichle & Snyder, 2007; Raichle et al., 2001). Searching for joined activations in this 'default state', two meta-analyses of PET activation protocols with healthy subjects revealed that a network of frontal and parietal heteromodal associative cortices was more active at rest as compared to other cognitive tasks (Shulman et al., 1997; Mazoyer et al., 2001). Such evidence led to the assumption that the brain at rest is not silent. On the contrary Hence, the brain's activity at rest is characterized by spontaneous low frequency fluctuations, in the range of 0.01- 0.1 Hz, which can be detected in the blood oxygen level dependent (BOLD signal of the fMRI measurement in 'resting' conditions. These spontaneous BOLD fluctuations cannot be attributed to peripheral noise (e.g., cardiac and respiratory fluctuations, motion of the subject, etc.) but show synchronized activity with other functionally related brain regions (Cordes et al., 2000; Fox & Raichle, 2007). In

For Review Only

particular, it is suggested that the brain's baseline activity is organized in two widespread brain networks: an 'extrinsic' and an 'intrinsic' (Fox et al., 2005; Cordes et al., 2000; Fox & Raichle, 2007; Boly et al., 2007; Fransson, 2005; Golland et al., 2007; Tian et al., 2007). The 'extrinsic' system encompasses lateral fronto-parietal areas, resembling the brain activations during goal-directed behavior and it has been linked to cognitive processes of somatosensory (Boly et al., 2007; Bornhovd et al., 2002; Buchel et al., 2002), visual (Fuhrmann Alpert, Hein, Tsai, Naumer & Knight, 2008; Rees, 2007) and auditive (Fuhrmann Alpert, Hein, Tsai, Naumer & Knight, 2008) external sensory input. The 'intrinsic' system encompasses mainly medial brain areas, it is similar to the activity of the default network and has been associated with cognitive processes such as mind wandering or daydreaming (Mason et al., 2007; McKiernan, D'Angelo, Kaufman & Binder, 2006), mental imagery (Knauff, Fangmeier, Ruff & Johnson-Laird, 2003), inner speech and self-oriented thoughts (Lou et al., 2004; Goldberg, Harel & Malach, 2006).

The present study aimed to bridge the gap between our knowledge on default resting state neural networks as assessed by fMRI and their subjective cognitive counterparts. In our behavioral experiment, we showed a negative correlation between external and internal awareness scores in nearly 80% of the studied subjects (24 out of 31 participants). It should be noted that despite the significant anticorrelation between external and internal modes of conscious processing at the group level there seems to exist a substantial variability at the individual subject level. Future studies could correlate this variability of conscious content with personality traits (e.g., from normal controls to "schizoid" subjects with dissociative contents of consciousness). We also showed a periodic shift from external to internal awareness occurring on average every 20 seconds (0.05 Hz), corresponding to the spontaneous low frequency fluctuations (range of 0.01- 0.1 Hz) previously reported (Cordes et al., 2000; Fox & Raichle, 2007). Engagement to demanding self-oriented tasks makes us

For Review Only

less receptive to environmental stimuli (James, 1890) and this switch in attention can happen without conscious recognition (Smallwood & Schooler, 2006). In absence of conscious control, human minds like to wander during both resting periods and heavily loaded cognitive tasks (Giambra, 1995; Antrobus, 1968). Such stimulus independent thoughts are reported significantly more often during rest than when performing externally oriented tasks (e.g., tone detection task; Filler & Giambra, 1973) and during tasks that are overlearned as compared to novel ones (Goldberg, Harel & Malach, 2006). This unconstrained mental activity was shown to impair signal detection (Giambra, 1995; Singer, 1993), reading (Antrobus, 1968), detailed encoding (Teasdale et al., 1995) and sustained attention tasks (Duval & Wicklund, 1972). In this sense, psychological research suggests that deprivation of external sensory input may result in an increase of internally generated activity (Giambra, 1995; Schooler, 2002; Schooler, Reichle & Halpern, 2005; Smallwood, McSpadden & Schooler, 2008). However, clinical cases such as Charles-Bonnet syndrome (i.e., visually impaired patients that experience visual illusions) might counterbalance these findings (Kester, 2009).

Our fMRI study showed a link between the intrinsic and extrinsic brain networks and spontaneous mentation. In the fMRI experiment, subjects' reports of being 'strongly externally aware' correlated with activation in the 'extrinsic system' (i.e., lateral fronto-parietal areas) and reports of being 'strongly internally aware' correlated with activation in the 'intrinsic system' (i.e., medial brain areas). Our data are in line with previous studies showing the competing character of the two systems in the sense that these two systems can disturb or even interrupt one another (Tian et al., 2007; Weissman, Roberts, Visscher & Woldorff, 2006), illustrated also by studies on motor performance (Fox, Snyder, Vincent & Raichle, 2007), perceptual discrimination (Sapir, d'Avossa, McAvoy, Shulman & Corbetta, 2005), attention lapses (Weissman, Roberts, Visscher & Woldorff, 2006), and somatosensory perception of stimuli close to sensory threshold (Boly et al., 2007). These studies have shown

For Review Only

that high pre-stimulus baseline activity in the ‘intrinsic’ system is associated with a tendency to ignore environmental stimuli whereas perceived external stimuli were associated with an increased activity in the ‘extrinsic’ system. The predictive value of the pre-stimulus baseline activity to behavior has been also shown by studies with EEG (Sapir, d’Avossa, McAvoy, Shulman & Corbetta, 2005) and magnetoencephalography (Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi & Palva, 2004). It should be noted that to date no definite answer can be given as to whether these two systems constitute the causal correlates of internal and external awareness. The sufficiency and necessity of these two components to consciousness remains to be further explored by, for example, transcranial magnetic stimulation (TMS) lesional protocols or other more invasive methodologies.

Although it has been suggested that the low frequency fluctuations observed at resting state reflect nothing but vascular processes (Lame, 2003), others support that they refer to conscious mentation (Goldberg, Harel & Malach, 2006). According to our results, collected via a semi-structured interview, the content of spontaneous thought was preferentially autobiographical and referred to mental images, reminiscence of past experiences and plan making, which correspond to accumulating data that the default network is mediating self-related processes (Sapir, d’Avossa, McAvoy, Shulman & Corbetta, 2005; Naghavi & Nyberg, 2005; Mitchell et al., 2007; Hester, Foxe, Molholm, Shpaner & Garavan, 2005; Li, Yan, Berquist & Sinha, 2007; Otten & Rugg, 2001; Golland, Golland, Bentin & Malach, 2008; Addis, Wong & Schacter, 2007). Several other explanations have been introduced for the functional role of the resting state, such that it reflects spontaneous thoughts (Buckner & Carroll, 2007) or that it accounts for the monitoring of the external world (for a review see Hahn, Ross & Stein, 2007). Nevertheless, the pervasiveness of the default network after general anesthesia in monkeys (Vincent et al., 2007), in vegetative state (only cortico-cortical connectivity) and its absence in brain death (Boly et al., 2009), reflects a fundamental intrinsic

For Review Only

property of the brain's organization that seems to transcend the levels of consciousness (Boly et al., 2009; Buckner, Andrews-Hanna & Schacter, 2008). Future studies could apply the presented methodology to modified states of consciousness such as hypnosis. We hypothesize that in hypnotic resting state, internal and external modes would be dissociated with a predominance of intrinsic network activity.

The critical role of the 'extrinsic' and 'intrinsic' systems to consciousness is well illustrated in cases of impaired conscious states. For example, in the vegetative state (a state of arousal without awareness, Laureys, 2005), systematic metabolic dysfunctions have been identified in a wide frontoparietal network encompassing bilateral lateral and frontal regions, bilateral parieto-temporal and posterior parietal areas, posterior cingulate cortex and precuneus (Laureys, 2005; Laureys et al., 1999). In addition, disconnections between latero-frontal and midline posterior areas and between thalamic nuclei and lateral and medial frontal cortices have been also found in vegetative patients (Laureys et al., 1999; 2000). The lack of external and internal awareness is observed not only in these patients, but also in slow-wave sleep (Maquet et al., 2005) and in general anesthesia (Kaisti et al., 2003) whereas they resume their functionality during REM-sleep (Maquet et al., 2005), supporting our findings.

In conclusion, our data shed light on the neural correlates of awareness' two major dimensions: external or environmental awareness relating to activity in lateral fronto-parietal associative networks - and internal awareness relating to midline "default" networks. The study of the functional integrity of these two interdependent brain networks may offer clinical interest in our search for neural markers of awareness in heath and disease (e.g., coma and related "vegetative" states).

For Review Only

ACKNOWLEDGMENTS

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth and the University of Liège. A.V. was funded by ARC 06/11-340, A.D. by the DISCOS Marie-Curie Research Training Network, M.B. is research fellow at the FNRS, Q.N. is a post-doctoral fellow at the FNRS, S.L. and C.P. are senior research associate at the FNRS.

For Review Only

REFERENCES

Addis, DR., Wong, AT. & Schacter, DL. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia, 45*, 1363-1377.

Antrobus, JL. (1968). Information theory and stimulus independent thought. *Br J Psychol, 59,* 423-430.

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., et al. (2007). Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc Natl Acad Sci USA, 104*, 12187-12192.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D. et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping,* in press.

Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., & Buchel, C. (2002). Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain, 125*, 1326-1336.

Buchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B., & Weiller, C. (2002). Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. *J Neurosci, 22,* 970-976.

Buckner, RL. & Carroll, DC. (2007). Self-projection and the brain. *Trends Cogn Sci, 11*, 49-57.

Buckner, RL., Andrews-Hanna, JR. & Schacter, DL. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38.

For Review Only

Cordes, D., Haughton, VM., Arfanakis, K., Wendt, GJ., Turski, PA., Moritz, CH., et al. (2000). Mapping functionally related regions of brain with functional connectivity MR imaging. *AJNR Am J Neuroradiol, 21*, 1636-1644.

Dehaene, S., Naccache, L., Cohen, L., Bihan, D. L., Mangin, J. F., Poline, J. B., et al. (2001).Cerebral mechanisms of word masking and unconscious repetition priming. *Nat Neurosci, 4*, 752-758.

Duval, TS. & Wicklund, RA. (1972). *A theory of objective self-awareness* (Academic, New York).

Filler, MS. & Giambra, LM. (1973). Daydreaming as a function of cueing and task difficulty. *Percept Mot Skills, 37*, 503-509.

Fox, M., Snyder, A., Vincent, J., Corbetta, M., Van Essen, D., & Raichle, M. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A, 102*, 9673-9678.

Fox, MD. & Raichle, ME. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci, 8*, 700-711.

Fox, MD., Snyder, AZ., Vincent, JL., & Raichle, ME. (2007). Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron, 56*, 171-184.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping, 26*, 15-29.

Friston, K., Ashburner, J., Frith, C., Poline, JB., Heather, J., & Frackowiak, RSJ. (1995a). Spatial registration and normalization of images. *Human Brain Mapping, 3*, 165-189.

Friston, K., Holmes, AP., Poline, JB., Grasby, PJ., Williams, SC., Frackowiak, R.S. et al. (1995b). Analysis of fMRI time-series revisited. *Neuroimage, 2*, 45-53.

For Review Only

Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, Poline J. (2000). To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. *Neuroimage* 12(2):196-208.

Friston KJ, Stephan KE, Lund TE, Morcom A, Kiebel S. (2005). Mixed-effects and fMRI studies. *Neuroimage* 24 (1):244-52.

Fuhrmann Alpert, G., Hein, G., Tsai, N., Naumer, MJ. & Knight, RT. (2008). Temporal characteristics of audiovisual information processing. *J Neurosci, 28*, 5344-5349.

Giambra, LM. (1995). A laboratory method for investigating influences on switching attention to task-unrelated imagery and thought. *Conscious Cogn, 4*, 1-21.

Goldberg, II, Harel, M., & Malach, R. (2006). When the brain loses its self: prefrontal inactivation during sensorimotor processing. *Neuron, 50*, 329-339.

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., et al. (2007). Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. *Cereb Cortex, 17,* 766-777.

Golland, Y., Golland, P., Bentin, S. & Malach, R. (2008). Data-driven clustering reveals a fundamental subdivision of the human cortex into two global systems. *Neuropsychologia, 46*, 540-553.

Hahn, B., Ross, TJ. & Stein, EA. (2007). Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cereb Cortex, 17*, 1664-1671.

Haynes, JD., Driver, J., & Rees, G. (2005).Visibility reflects dynamic changes of effective connectivity between V1 and fusiform cortex. *Neuron, 46*, 811-821.

Hester, R., Foxe, JJ., Molholm, S., Shpaner, M. & Garavan, H. (2005). Neural mechanisms involved in error processing: A comparison of errors made with and without awareness. *Neuroimage, 27*, 602-608.

For Review Only

James, W. (1890). in *The Principles of Psychology* (Dover Publications, New York), pp. 402-458.

Kaisti, KK., Langsjo, JW., Aalto, S., Oikonen, V., Sipila, H., Teras, M., et al. (2003). Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology, 99,* 603-613.

Kester EM. 2009. Charles Bonnet syndrome: case presentation and literature review. Optometry 80(7):360-6.

Knauff, M., Fangmeier, T., Ruff, CC. & Johnson-Laird, PN. (2003). Reasoning, models, and images: behavioral measures and cortical activity. *J Cogn Neurosci, 15*, 559-573.

Laguna P., Moody GB., Mark RG., (1998) Power spectral density of unevenly sampled data by least-square analysis: performance and application to heart rate signals, *IEEE Trans Biomed Eng,* 45(6):698-715.

Lamme, VA. (2003). Why visual attention and awareness are different. *Trends Cogn Sci, 7*, 12-18.

Laureys, S. (2005). The neural correlate of (un)awareness: lessons from the vegetative state. *Trends Cogn Sci, 9*, 556-559.

Laureys, S., Faymonville, ME., Luxen, A., Lamy, M., Franck, G., & Maquet, P. (2000). Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*, *355***,** 1790-1791.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A. et al. (1999). Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage, 9,* 377-382.

Laureys, S., Perrin, F. & Bredart, S. (2007).Self-consciousness in non-communicative patients. *Conscious Cogn, 16,* 722-741.

For Review Only

Li, CS., Yan, P., Bergquist, KL., & Sinha, R. (2007). Greater activation of the "default" brain regions predicts stop signal errors. *Neuroimage, 38*, 640-648.

Lieberman, M. (2007). Social cognitive neuroscience: a review of core processes. *Annu Rev Psychol, 58*, 259-289.

Linkenkaer-Hansen, K., Nikulin, VV., Palva, S., Ilmoniemi, RJ., & Palva, JM. (2004). Prestimulus oscillations enhance psychophysical performance in humans. *J Neurosci, 24*, 10186-10190.

Lomb, N. (1976). Least-squares frequency analysis of unequally spaced data. *Astrophys Space Sci, 39***,** 447-462.

Lou, HC., Luber, B., Crupain, M., Keenan, JP., Nowak, M., Kjaer, TW. et al. (2004). Parietal cortex and representation of the mental Self. *Proc Natl Acad Sci U S A, 101***,** 6827-6832.

Lutz, A., Lachaux, J. P., Martinerie, J., & Varela, F. J. (2002). Guiding the study of brain dynamics by using first-person data: synchrony patterns correlate with ongoing conscious states during a simple visual task. *Proc Natl Acad Sci U S A*, 99(3), 1586-1591.

Maquet, P., Ruby, P., Maudoux, A., Albouy, G., Sterpenich, V., Dang-Vu, T. et al. (2005). Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. *Prog Brain Res, 150***,** 19-227.

Mason, MF., Norton, MI., Van Horn, JD., Wegner, DM., Grafton, ST. & Macrae, C.N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science, 315,* 393-395.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O. et al. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull, 54*, 287-298.

For Review Only

McKiernan, KA., D'Angelo, BR., Kaufman, JN. & Binder, JR. (2006). Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage, 29***,** 1185-1191.

Mikl, M., Marecek, R., Hlustik, P., Pavlicova, M., Drastich, A., Chlebus, P., et al., (2008). Effects of spatial smoothing on fMRI group inferences. *Magn. Reson. Imaging 26 (4),* 490–503.

Mitchell, JP., Heatherton TF., Kelley WM., Wyland CL., Wegner DM., Neil Macrae C. (2007). Separating sustained from transient aspects of cognitive control during thought suppression. *Psychol Sci, 18*, 292-297.

Naghavi, HR. & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? *Conscious Cogn, 14*, 390-425.

Otten, LJ. & Rugg, MD. (2001). When more means less: neural activity related to unsuccessful memory encoding. *Curr Biol, 11*, 1528-1530.

Peigneux, P., Orban, P., Balteau, E., Degueldre, C., Luxen, A., Laureys, S. et al. (2006). Offline persistence of memory-related cerebral activity during active wakefulness. *PLoS Biol, 4,*100.

Penny, W. & Holmes, A. (2003). in *Human brain function*, eds. Frackowiak, R., Friston, K., Frith, C., Dolan, R., Price, C., Zeki, S., Ashburner, J., & Penny, W. (Academic Press, London).

Press, W., Flannery, B., Teukolsky, S., & Vetterling, W. (1992). in *Numerical Recipes in C* (Cambridge University press), pp. 575-583.

Raichle, ME. & Snyder, AZ. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37***,** 1083-1090; discussion 1097-1089.

Raichle, ME., MacLeod, AM., Snyder, AZ., Powers, WJ., Gusnard, DA. & Shulman, GL. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98,* 676-682.

For Review Only

Rees, G. (2007). Neural correlates of the contents of visual awareness in humans. *Philos Trans R Soc Lond B Biol Sci., 362***,** 877-886.

Sapir, A., d'Avossa, G., McAvoy, M., Shulman, GL., & Corbetta, M. (2005). Brain signals for spatial attention predict performance in a motion discrimination task. *Proc Natl Acad Sci U S A, 102*, 17810-17815.

Schooler, JW. (2002). Re-representing consciousness: dissociations between experience and meta-consciousness. *Trends Cogn Sci, 6***,** 339-344.

Schooler, JW., Reichle, ED. & Halpern, DV. (2005). in *Thinking and seeing: Visual metacognition in adults and children.*, ed. Levin, D. T. (MIT Press, Cambridge: MA), pp. 204-226.

Shulman, GL., Fiez, JA., Corbetta, M., Buckner, RL., Miezin, FM., Raichle, ME., et al. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J Cogn Neurosci, 9***,** 648-663.

Singer, JL. (1993). Experimental studies of ongoing conscious experience. *Ciba Found Symp*, 174, 100-116; discussion 116-122.

Smallwood, J. & Schooler, JW. (2006). The restless mind. *Psychol Bull, 132,* 946-958.

Smallwood, J., McSpadden, M. & Schooler, J. W. (2008). When attention matters: the curious incident of the wandering mind. *Mem Cognit, 36***,** 1144-1150.

Teasdale, JD. , Dritschel, BH., Taylor, MJ., Proctor, L., Lloyd, CA., Nimmo-Smith, I. et al. (1995). Stimulus-independent thought depends on central executive resources. *Mem Cognit, 23***,** 551-559.

Tian, L., Jiang, T., Liu, Y., Yu, C., Wang, K., Zhou, Y., et al. (2007). The relationship within and between the extrinsic and intrinsic systems indicated by resting state correlational patterns of sensory cortices. *Neuroimage, 36,* 684-690.

For Review Only

Vanhaudenhuyse, A., Boly, M., Balteau, E., Schnakers, C., Moonen, G., Luxen, A., Lamy, M., Degueldre, C., Brichantd, J.F., Maquet, P., Laureys, S., Faymonville, M.E (2009). Pain and non-pain processing during hypnosis: A thulium-YAG event-related fMRI study. *NeuroImage*, *47(3),* 1047-1054

Varela, F. J. (1996). Neurophenomenology: a methodological remedy for the hard problem. *Journal of Consciousness Studies*, 330-349.

Vincent, JL., Patel, GH., Fox, MD., Snyder, AZ., Baker, JT., Van Essen, DC.et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature, 447*, 83-86.

Vuilleumier, P., Sagiv, N., Hazeltine, E., Poldrack, RA., Swick, D., Rafal, RD., & Gabrieli, JD. et al. (2001). Neural fate of seen and unseen faces in visuospatial neglect: a combined event-related functional MRI and event-related potential study. *Proc Natl Acad Sci U S A, 98***,** 3495-3500.

Weissman, DH., Roberts, K., Visscher, K., & Woldorff, MG. (2006). The neural bases of momentary lapses in attention. *Nat Neurosci., 9***,** 971-978.

White, T., O'Leary, D., Magnotta, V., Arndt, S., Flaum, M., Andreasen, N.C., (2001). Anatomic and functional variability: the effects of filter size in group fMRI data analysis. *NeuroImage 13 (4),* 577–588.

Worsley, K. J. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4***,** 58-73.

Zeman, A. (2001). Consciousness. *Brain, 124*, 1263-1289.

For Review Only

TABLES

Table 1

The contents of the two components of awareness based on semi-structured interview after completion of the behavioral experiment.

	Content	Number of subjects (%)	Examples
External	Auditory	20 (65%)	Hearing sounds from outside the room
	Somesthetic	18 (58%)	Felt itchiness, uncomfortable body posture
	Olfactory	4 (13%)	Smelling perfume
	Visual	2 (1%)	Visual perceptions through closed eyelids
Internal	Experiment-related	16 (52%)	Thoughts related to the length of the study
	Autobiographical (future & past)	13 (42%)	Vacation, plans for weekend
	Inner speech	4 (13%)	Instruction to oneself to stay vigilant

For Review Only

Table 2

Peak voxels of brain areas showing a positive correlation with intensity of external and internal awareness.

Region	***x* (mm)**	***y* (mm)**	***z* (mm)**	**z-value**	**p-value**
A. INTERNAL					
PCC/precuneus	-10	-42	8	4.68	< 0.0001**
ACC/mesiofrontal	-12	20	38	5.01	< 0.0001**
Left parahippocampal	-24	-18	-20	3.87	< 0.0001**
Right parahippocampal	38	-30	-10	4.76	< 0.0001**
B. EXTERNAL					
R inferior frontal gyrus	38	44	4	2.66	0.004*
L inferior frontal gyrus	-36	32	16	2.25	NS (0.012)
R inferior parietal	60	-42	32	2.86	0.002*
L inferior parietal	-58	-30	22	2.49	NS (0.006)

***False discovery rate corrected; *Small volume corrected (8mm radius sphere centered on previously published coordinates) ; R: right; L: left; PCC: posterior cingulate cortex; ACC: anterior cingulate cortex; NS: non significant*

For Review Only

FIGURES LEGEND

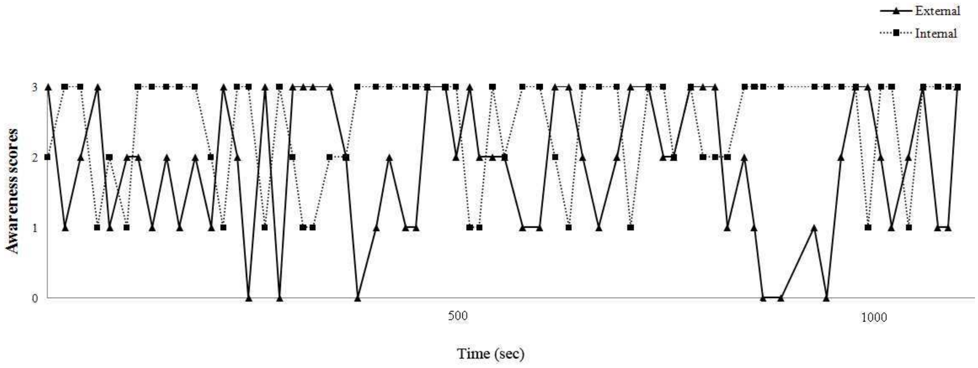
Figure 1

The temporal dynamics of the two components of awareness in a representative subject illustrating that external and internal awareness scores anticorrelate.

Figure 2

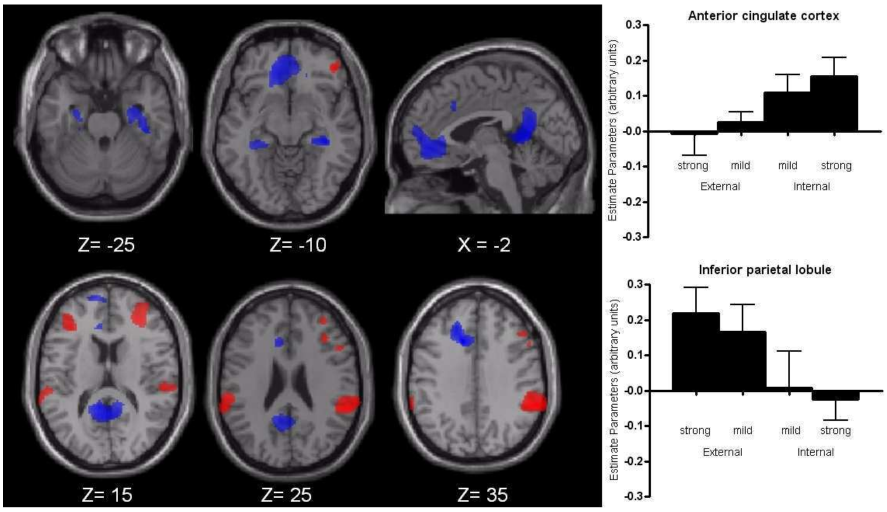
Brain regions showing a correlation between BOLD signal and the intensity of internal and external awareness scores in 22 healthy volunteers. Stronger internal awareness scores correlate with increased activity in anterior cingulate/mesiofrontal, posterior cingulate/precuneal, and parahippocampal cortices (areas in blue). External awareness scores correlate with increased activity in bilateral inferior parietal lobule and dorsolateral prefrontal cortices (in red).

For Review Only



The temporal dynamics of the two components of awareness in a representative subject illustrating that external and internal awareness scores anticorrelate.
305x115mm (96 x 96 DPI)

Review Only



Brain regions showing a correlation between BOLD signal and the intensity of internal and external awareness scores in 22 healthy volunteers. Stronger internal awareness scores correlate with increased activity in anterior cingulate/mesiofrontal, posterior cingulate/precuneal, and parahippocampal cortices (areas in blue). External awareness scores correlate with increased activity in bilateral inferior parietal lobule and dorsolateral prefrontal cortices (in red).
158x82mm (200 x 200 DPI)

ew Only

The NEW ENGLAND JOURNAL of MEDICINE

Willful Modulation of Brain Activity in Disorders of Consciousness

Martin M. Monti, Ph.D., Audrey Vanhaudenhuyse, M.Sc., Martin R. Coleman, Ph.D., Melanie Boly, M.D.,
John D. Pickard, F.R.C.S., F.Med.Sci., Luaba Tshibanda, M.D., Adrian M. Owen, Ph.D., and Steven Laureys, M.D., Ph.D.

ABSTRACT

BACKGROUND

The differential diagnosis of disorders of consciousness is challenging. The rate of misdiagnosis is approximately 40%, and new methods are required to complement bedside testing, particularly if the patient's capacity to show behavioral signs of awareness is diminished.

METHODS

At two major referral centers in Cambridge, United Kingdom, and Liege, Belgium, we performed a study involving 54 patients with disorders of consciousness. We used functional magnetic resonance imaging (MRI) to assess each patient's ability to generate willful, neuroanatomically specific, blood-oxygenation-level–dependent responses during two established mental-imagery tasks. A technique was then developed to determine whether such tasks could be used to communicate yes-or-no answers to simple questions.

RESULTS

Of the 54 patients enrolled in the study, 5 were able to willfully modulate their brain activity. In three of these patients, additional bedside testing revealed some sign of awareness, but in the other two patients, no voluntary behavior could be detected by means of clinical assessment. One patient was able to use our technique to answer yes or no to questions during functional MRI; however, it remained impossible to establish any form of communication at the bedside.

CONCLUSIONS

These results show that a small proportion of patients in a vegetative or minimally conscious state have brain activation reflecting some awareness and cognition. Careful clinical examination will result in reclassification of the state of consciousness in some of these patients. This technique may be useful in establishing basic communication with patients who appear to be unresponsive.

From the Medical Research Council Cognition and Brain Sciences Unit (M.M.M., A.M.O.), the Impaired Consciousness Study Group, Wolfson Brain Imaging Centre, University of Cambridge (M.R.C.), and the Division of Academic Neurosurgery, Addenbrooke's Hospital (J.D.P.) — all in Cambridge, United Kingdom; and the Coma Science Group, Cyclotron Research Center, University of Liege (A.V., M.B., S.L.), and the Departments of Neurology (S.L., M.B.) and Neuroradiology (L.T.), University Hospital of Liege, Liege; and Fonds de la Recherche Scientifique, Brussels (A.V., S.L., M.B.) — all in Belgium. Address reprint requests to Dr. Owen at the Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Rd., Cambridge CB2 7EF, United Kingdom, or at adrian.owen@mrc-cbu.cam.ac.uk.

Dr. Monti and Ms. Vanhaudenhuyse contributed equally to this article.

This article (10.1056/NEJMoa0905370) was published on February 3, 2010, at NEJM.org.

N Engl J Med 2010.

Copyright © 2010 Massachusetts Medical Society.

In recent years, improvements in intensive care have led to an increase in the number of patients who survive severe brain injury. Although some of these patients go on to have a good recovery, others awaken from the acute comatose state but do not show any signs of awareness. If repeated examinations yield no evidence of a sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli, a diagnosis of a vegetative state — or "wakefulness without awareness" — is made.[1-5] Some patients remain in a vegetative state permanently. Others eventually show inconsistent but reproducible signs of awareness, including the ability to follow commands, but they remain unable to communicate interactively. In 2002, the Aspen Neurobehavioral Conference Work Group coined the term "minimally conscious state" to describe the condition of such patients, thereby adding a new clinical entity to the spectrum of disorders of consciousness.[6]

There are two main goals in the clinical assessment of patients in a vegetative or minimally conscious state. The first goal is to determine whether the patient retains the capacity for a purposeful response to stimulation, however inconsistent. Such a capacity, which suggests at least partial awareness, distinguishes minimally conscious patients from those in a vegetative state and therefore has implications for subsequent care and rehabilitation, as well as for legal and ethical decision making. Unfortunately, the behavior elicited from these patients is often ambiguous, inconsistent, and constrained by varying degrees of paresis, making it very challenging to distinguish purely reflexive from voluntary behaviors. Nevertheless, in the absence of an absolute measure, awareness has to be inferred from a patient's motor responsiveness; this fact undoubtedly contributes to the high rate of diagnostic errors (approximately 40%) in this group of patients.[7-9]

The second goal of clinical assessment is to harness and nurture any available response, through intervention, into a form of reproducible communication, however rudimentary. The acquisition of any interactive and functional verbal or nonverbal method of communication is an important milestone. Clinically, consistent and repeatable communication demarcates the upper boundary of a minimally conscious state.[6]

In this article, we present the results of a study conducted between November 2005 and January 2009 in which functional magnetic resonance imaging (MRI) was routinely used in the evaluation of a group of 54 patients with a clinical diagnosis of being in a vegetative state or a minimally conscious state. In light of a previous single-case study that showed intact awareness in a patient who met the clinical criteria for being in a vegetative state,[10] our investigation had two main aims. The first aim was to determine what proportion of this group of patients could also reliably and repeatedly modulate their functional MRI responses, reflecting preserved awareness. The second aim was to develop and validate a method that would allow such patients to functionally communicate yes-or-no responses by modulating their own brain activity, without training and without the need for any motor response.

METHODS

PATIENTS

A convenience sample of 54 patients with severe brain injury, including 23 in a vegetative state and 31 in a minimally conscious state, underwent functional MRI as a means of evaluating their performance on motor and spatial imagery tasks. Characteristics of the patients are shown in Table 1, and the inclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Written informed consent was obtained from the legal guardians of all patients. The motor and spatial imagery tasks have been well validated in healthy control subjects[10-12] and are known to be associated with distinct functional MRI activity in the supplementary motor area and the parahippocampal gyrus.

The method to detect functional communication was first tested for feasibility and robustness in 16 healthy control subjects (9 men and 7 women) with no history of a neurologic disorder. Once validated, the tasks were given to one patient (Patient 23 in Table 1 and Fig. 1), who had received a diagnosis of being in a permanent vegetative state 17 months after a traffic accident;

this diagnosis was confirmed by a month-long specialized assessment 3.5 years after the injury. At the time of admission for functional MRI scanning (5 years after the ictus), the patient was assumed to remain in a vegetative state, although extensive behavioral testing after the functional MRI revealed reproducible, but inconsistent, responses indicative of a minimally conscious state. (The Supplementary Appendix includes detailed results and a description of the clinical assessment of this patient.)

IMAGERY TASKS

While in the functional MRI scanner, all patients were asked to perform two imagery tasks. In the motor imagery task, they were instructed to imagine standing still on a tennis court and to swing an arm to "hit the ball" back and forth to an imagined instructor. In the spatial imagery task, participants were instructed to imagine navigating the streets of a familiar city or to imagine walking from room to room in their home and to visualize all that they would "see" if they were there. First, two so-called localizer scanning sessions were conducted in which the patients were instructed to alternate 30-second periods of mental imagery with 30-second periods of rest. Each scan included five rest–imagery cycles. The beginning of each imagery period was cued with the spoken word "tennis" or "navigation," and rest periods were cued with the word "relax."

COMMUNICATION TASK

After the localizer scans had been obtained, all 16 control subjects and 1 patient underwent functional MRI during which they attempted to answer questions by modulating their brain activity, and a set of so-called communication scans were obtained. Before each of these imaging sessions, participants were asked a yes-or-no question (e.g., "Do you have any brothers?") and instructed to respond during the imaging session by using one type of mental imagery (either motor imagery or spatial imagery) for "yes" and the other for "no." The nature of the questions ensured that the investigators would not know the correct answers before judging the functional MRI data. Participants were asked to respond by thinking of whichever imagery corresponded to the answer that they wanted to convey. Communication scanning was identical to localizer scanning with the exception that the same neutral word "answer" was used to cue each response to a question (with "relax" used as the cue for rest periods). Cues were delivered once, at the beginning of each period. Three communication scans (with one question per scan) were obtained for each of the 16 healthy control subjects. To maximize statistical power, six communication scans (with one question per scan) were obtained for the patient.

STATISTICAL ANALYSIS

Analyses were performed with the use of FSL software, version 4.1.[13] Data analysis included standard functional MRI preprocessing steps (functional MRI acquisition and preprocessing are described in the Supplementary Appendix). For each scan, a general linear model contrasting periods of active imagery with periods of rest was computed. All contrasts were limited to the brain locations within the supplementary motor area and the parahippocampal gyrus, as defined in the Harvard–Oxford Cortical Structural Atlas (available in FSL software), and a threshold was established, with gaussian random-fields theory, at a cluster-level z value of more than 2.3 (corrected $P<0.05$). The defined regions of interest were transformed from standard space (according to the criteria of the Montreal Neurological Institute) to fit each subject's structural image, with the use of a method involving 12 degrees of freedom.

To determine whether the imagery tasks produced the expected activations in predefined neuroanatomical locations, two scans were compared for each participant: motor imagery and spatial imagery. The multiple localizer scanning sessions of the patient who also underwent communication scanning were averaged with the use of a fixed-effects model.

Answers provided during the communication scanning were assessed with the use of a two-step procedure. First, activity in the two regions of interest (the supplementary motor area and the parahippocampal gyrus) identified during the localizer scanning was quantitatively characterized (with the use of the average generalized linear model estimate for each region of interest).

Table 1. Characteristics of the Patients.*

Patient No.	Location	Age	Sex	Diagnosis on Admission	Cause of Disorder	Interval since Ictus	Response on Motor Imagery Task	Response on Spatial Imagery Task
		yr				*mo*		
1	Cambridge	58	Male	VS	TBI	6.0	No	No
2	Cambridge	43	Female	VS	Anoxic brain injury	50.0	No	No
3	Cambridge	41	Female	VS	TBI	10.0	No	NA
4	Cambridge	23	Female	VS	TBI	6.0	Yes	Yes
5	Cambridge	42	Male	VS	Anoxic brain injury	8.0	No	No
6	Cambridge	46	Male	VS	TBI	2.0	Yes	No
7	Cambridge	52	Female	VS	Anoxic brain injury, encephalitis	8.0	No	NA
8	Cambridge	23	Male	VS	TBI	19.0	No	No
9	Cambridge	48	Female	VS	Anoxic brain injury	18.0	No	No
10	Cambridge	34	Male	VS	TBI	13.0	No	No
11	Cambridge	35	Male	VS	Anoxic brain injury	10.0	No	No
12	Cambridge	29	Male	VS	TBI	11.0	No	No
13	Cambridge	67	Male	VS	TBI	14.0	No	No
14	Cambridge	21	Male	VS	TBI	6.0	No	No
15	Cambridge	49	Male	VS	TBI	3.0	No	NA
16	Cambridge	56	Female	VS	Anoxic brain injury	9.0	No	No
17	Liege	87	Male	VS	CVA	<1.0	No	No
18	Liege	62	Male	VS	CVA	1.0	No	No
19	Liege	15	Male	VS	Anoxic brain injury, TBI	20.5	No	No
20	Liege	70	Female	VS	Meningitis	2.5	No	No
21	Liege	47	Male	VS	Anoxic brain injury	18.8	No	No
22	Liege	22	Female	VS	TBI	30.2	Yes	Yes
23†	Liege	22	Male	VS	TBI	60.8	Yes	Yes
24	Cambridge	23	Male	MCS	TBI	11.0	No	No
25	Cambridge	38	Female	MCS	TBI	3.0	No	NA
26	Cambridge	18	Male	MCS	TBI	8.0	No	No
27	Cambridge	26	Male	MCS	TBI	11.0	No	NA
28	Cambridge	64	Male	MCS	TBI	6.0	No	No
29	Cambridge	54	Female	MCS	Brain-stem stroke	5.0	No	No
30	Cambridge	29	Female	MCS	TBI	2.0	No	NA
31	Cambridge	19	Female	MCS	TBI	1.0	No	No
32	Cambridge	34	Male	MCS	TBI	52.0	No	NA
33	Cambridge	17	Male	MCS	TBI	7.0	No	NA
34	Cambridge	56	Male	MCS	Anoxic brain injury	6.0	No	No
35	Cambridge	21	Male	MCS	TBI	51.0	No	No
36	Cambridge	53	Female	MCS	Anoxic brain injury	13.0	No	No
37	Cambridge	36	Male	MCS	TBI	30.0	No	NA
38	Cambridge	25	Male	MCS	TBI	8.0	No	No

Table 1. (Continued.)

Patient No.	Location	Age	Sex	Diagnosis on Admission	Cause of Disorder	Interval since Ictus	Response on Motor Imagery Task	Response on Spatial Imagery Task
		yr				*mo*		
39	Liege	64	Female	MCS	Meningitis	<1.0	No	No
40	Liege	37	Male	MCS	TBI	11.4	No	No
41	Liege	70	Male	MCS	Meningitis	1.3	No	No
42	Liege	36	Male	MCS	TBI	4.5	No	No
43	Liege	49	Male	MCS	TBI	0.4	No	No
44	Liege	49	Male	MCS	TBI	1.6	No	No
45	Liege	19	Male	MCS	TBI	1.3	No	No
46	Liege	26	Male	MCS	Anoxic brain injury	42.4	No	No
47	Liege	49	Female	MCS	Anoxic brain injury	84.7	No	No
48	Liege	55	Male	MCS	Anoxic brain injury	1.0	No	No
49	Liege	28	Male	MCS	TBI	72.3	No	No
50	Liege	49	Female	MCS	Anoxic brain injury	84.7	No	No
51	Liege	49	Male	MCS	Anoxic brain injury	0.8	No	No
52	Liege	39	Male	MCS	Anoxic brain injury	308.9	No	No
53	Liege	23	Male	MCS	TBI	10.0	No	No
54	Liege	27	Male	MCS	TBI	1.3	Yes	Yes

* CVA denotes cerebrovascular accident, MCS minimally conscious state, NA not analyzed because of excessive movement, TBI traumatic brain injury, and VS vegetative state.

† Patient 23 was the only patient who underwent functional MRI to obtain a communication scan.

Next, a similarity metric (described in the Supplementary Appendix) was computed to quantify how closely the activity in the regions of interest on each communication scan matched each localizer scan.

RESULTS

RESPONSES TO THE IMAGERY TASKS

Among the 54 patients, we identified 5 who could willfully modulate their brain activity (Fig. 1). In all five of these patients, the functional MRI scans associated with motor imagery, as compared with spatial imagery, showed considerable activation in the supplementary motor area. In four of the five patients, the scans associated with spatial imagery, as compared with motor imagery, showed activation in the parahippocampal gyrus. Furthermore, the time course of activity within the two regions of interest was sustained for 30 seconds and was associated with the delivery of the verbal cues (Fig. 2). These results closely match the pattern observed in the healthy control subjects (Fig. 1, and the Supplementary Appendix). Four of the five patients were considered to be in a vegetative state (including Patient 4, who has been described previously[10]), and all five patients had a traumatic brain injury (Table 1).

RESPONSES TO THE COMMUNICATION TASK

Each of the 16 healthy control subjects underwent functional MRI to obtain three communication scans. For all 48 questions in the communication task, the correct answer was determined with 100% accuracy by comparing the activations shown on the communication scans with the activations shown on two localizer scans. In all subjects, the pattern produced in response to each question was quantitatively more similar to the pattern observed in the localizer scan for the imagery task that was associated with the factually correct answer; this answer was verified after the analysis. Figures 2B, 2D, 3B, and 3D show this similarity in a healthy control. In this subject, the

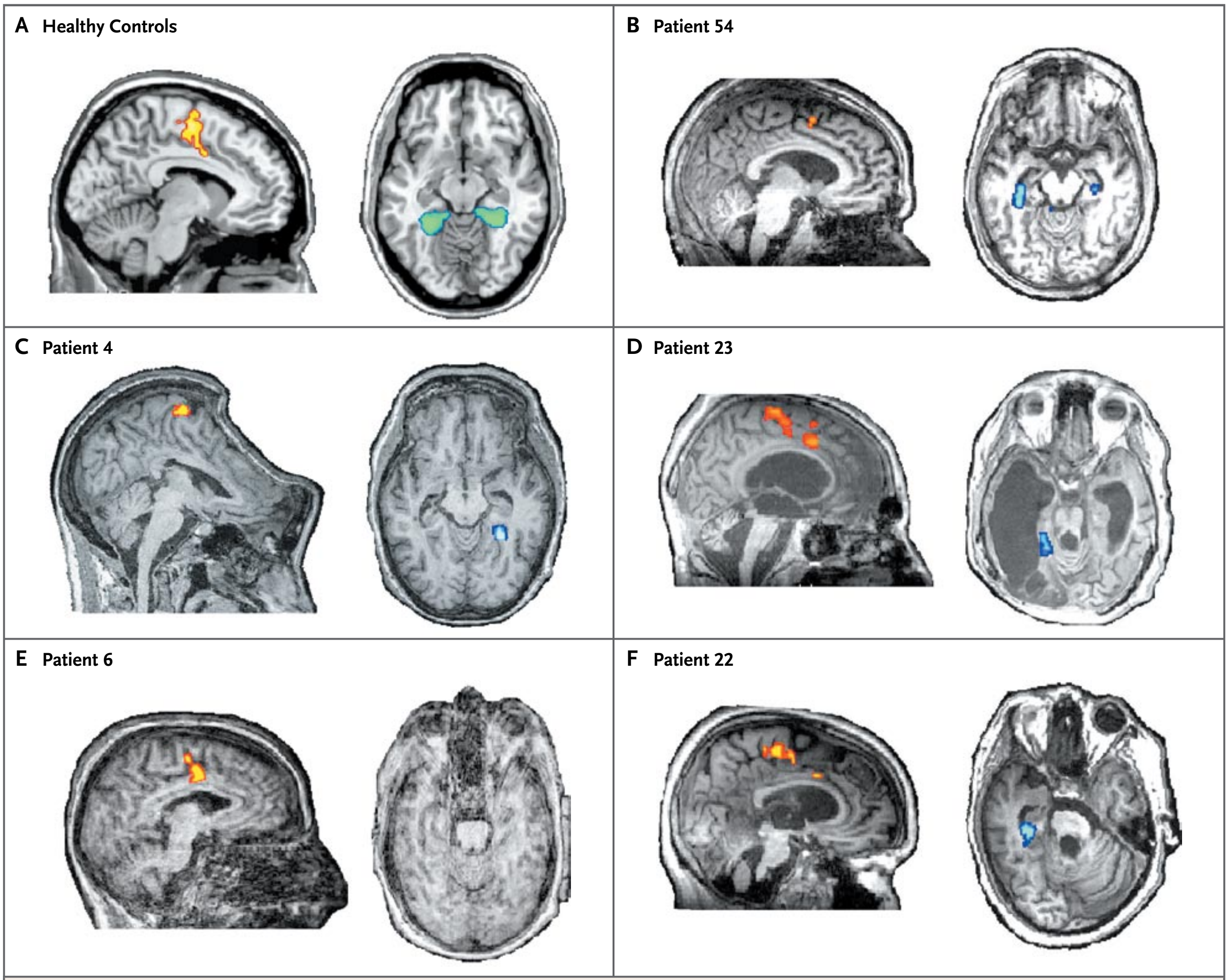


Figure 1. **Mental-Imagery Tasks.**

Functional MRI scans show activations associated with the motor imagery as compared with spatial imagery tasks (yellow and red) and the spatial imagery as compared with motor imagery tasks (blue and green). These scans were obtained from a group of healthy control subjects and five patients with traumatic brain injury.

activation associated with the imagery period as compared with the rest period for question 1 resulted in extensive activation in the supplementary motor area and minimal activity in the parahippocampal gyrus (Fig. 4). This pattern was almost identical to that observed in the activation associated with the motor imagery period as compared with the rest period in the motor localizer scan. Conversely, the imagery period as compared with the rest period for questions 2 and 3 was associated with extensive activation of the parahippocampal gyrus and, to a lesser extent, the supplementary motor area; these findings closely matched the activation seen in the spatial localizer scan. Similar patterns were observed in 9 of 16 control subjects. In the remaining seven control subjects, the distinction between tasks was even clearer; thus, a double dissociation was observed between activity in the supplementary motor area for motor imagery and activity in the parahippocampal gyrus for spatial navigation (see the Supplementary Appendix).

To assess whether such an approach could be used in a patient with impaired consciousness, one of the patients who had reliable responses during the two imagery tasks (Patient 23) was also asked six yes-or-no autobiographical questions and instructed to respond by thinking of one type of imagery (either motor imagery or spatial imagery) for an affirmative answer and the other type of imagery for a negative answer.

In this patient, the activity observed on the communication scan in response to five of the six questions closely matched that observed on one of the localizer scans (Fig. 2A, 2C, 3A, and 3C). For example, in response to the question “Is your father’s name Alexander?” the patient responded “yes” (correctly) with activity that matched that observed on the motor-imagery localizer scan (Fig. 3A). In response to the question “Is your father’s name Thomas?” the patient responded “no” (also correctly) with activity that matched that observed in the spatial-imagery localizer scan (Fig. 3C).

The relative-similarity analysis confirmed, quantitatively, that the activity observed on the communication scans accurately reproduced that observed on the localizer scans within the bounds of normal variability for five of the six questions (Fig. 4, and Tables A1 and A2 in the Supplementary Appendix). In addition, for those same five questions, the pattern produced always matched the factually correct answer. Only one question, the last one, could not be decoded. However, this was not because the “incorrect” pattern of activation was observed, but rather because virtually no activity was observed within the regions of interest.

DISCUSSION

In this study, functional MRI was used to determine the incidence of undetected awareness in a group of patients with severe brain injuries. Of the 54 patients, 5 with traumatic brain injuries were able to modulate their brain activity by generating voluntary, reliable, and repeatable blood-oxygenation-level–dependent responses in predefined neuroanatomical regions when prompted to perform imagery tasks. No such responses were observed in any of the patients with nontraumatic brain injuries. Four of the five patients who were able to generate these responses were admitted to the hospital with a diagnosis of being in a vegetative state. When these four patients were thoroughly retested at the bedside, some behavioral indicators of awareness could be detected in two of them. However, the other two patients remained behaviorally unresponsive at the bedside, even after the functional MRI results were known and despite repeated testing by a multidisciplinary team. Thus, in a minority of cases, patients who meet the behavioral criteria for a vegetative state have residual cognitive function and even conscious awareness.[14,15]

We conducted additional tests in one of the five patients with evidence of awareness on functional MRI, and we found that he had the ability to apply the imagery technique in order to answer simple yes-or-no questions accurately. Before the scanning was performed, the patient had undergone repeated evaluations indicating that he was in a vegetative state, including a month-long specialized assessment by a highly trained clinical team. At the time of scanning, however, thorough retesting at the bedside showed reproducible but highly fluctuating and inconsistent signs of awareness (see the Supplementary Appendix), findings that are consistent with the diagnosis of a minimally conscious state. Nonetheless, despite the best efforts of the clinical team, it was impossible to establish any functional communication at the bedside, and the results of the behavioral examination remained ambiguous and inconsistent. In contrast, the functional MRI approach allowed the patient to establish functional and interactive communication. Indeed, for five of the six questions, the patient had a reliable neural response and was able to provide the correct answer with 100% accuracy. For the remaining question — the last question of the imaging session — the lack of activity within the regions of interest precluded any analysis of the results. Whether the patient fell asleep during this question, did not hear it, simply elected not to answer it, or lost consciousness cannot be determined.

Although the functional MRI data provided clear evidence that the patient was aware and able to communicate, it is not known whether either ability was available during earlier evaluations. It is possible that he was in a vegetative state when the diagnosis was received at 17 months and again 3.5 years after injury and subsequently regained some aspects of cognitive functioning. Alternatively, the patient may have been aware during previous assessments but unable to produce the necessary motor response required to signal his state of consciousness. If this was the case, then the clinical diagnosis of

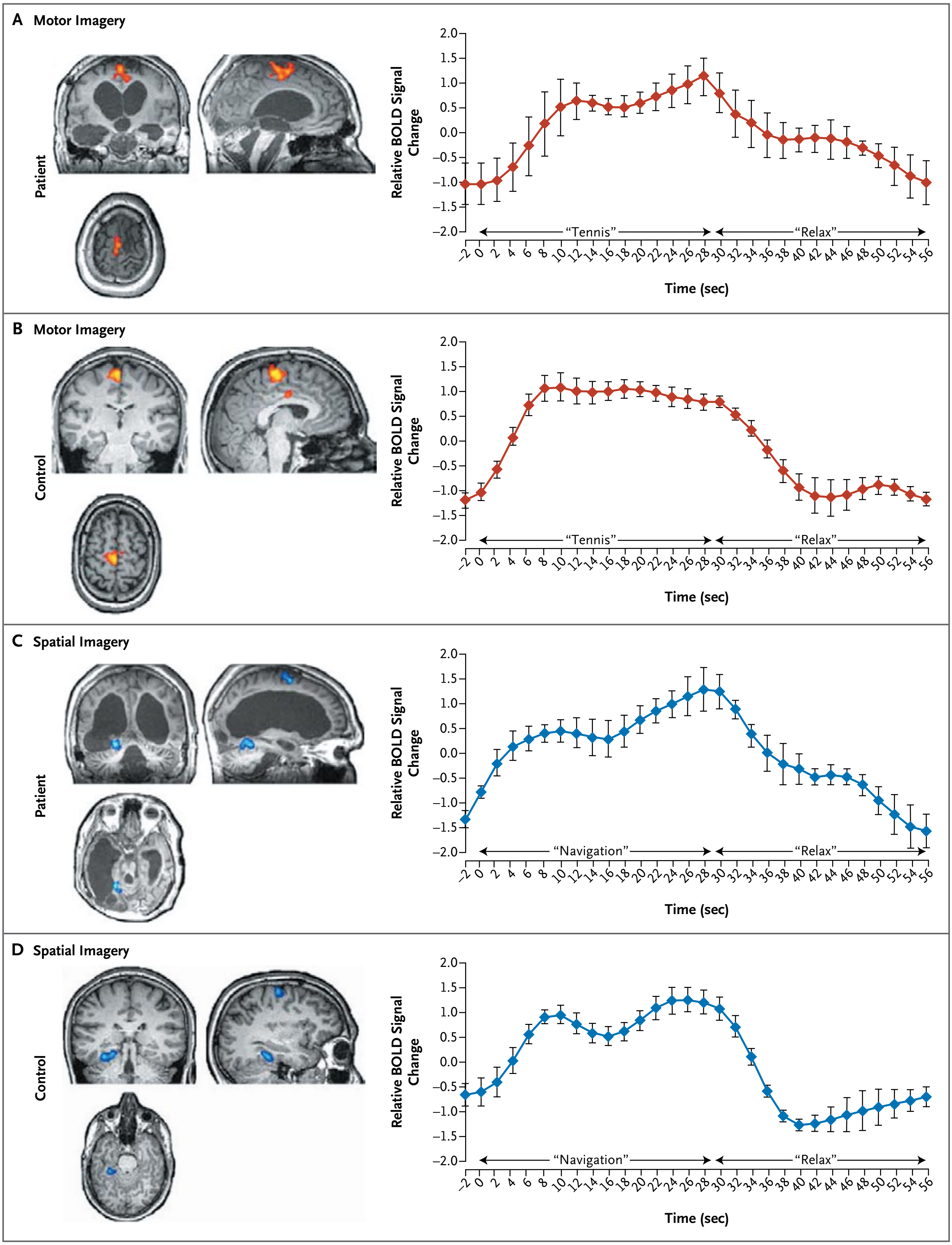
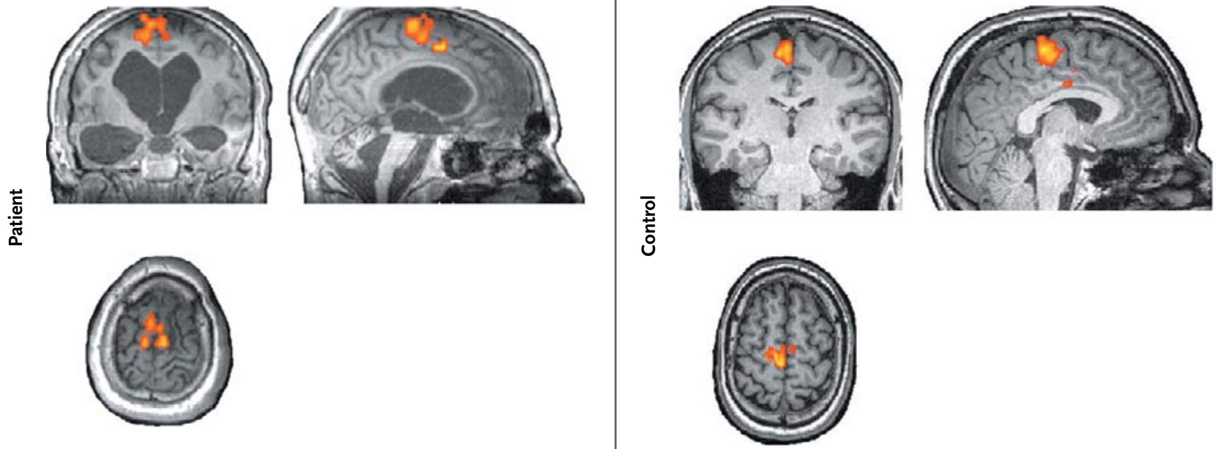

A Motor Imagery
Patient
Relative BOLD Signal Change
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
"Tennis"
"Relax"
−2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56
Time (sec)
B Motor Imagery
Control
Relative BOLD Signal Change
"Tennis"
"Relax"
Time (sec)
C Spatial Imagery
Patient
Relative BOLD Signal Change
"Navigation"
"Relax"
Time (sec)
D Spatial Imagery
Control
Relative BOLD Signal Change
"Navigation"
"Relax"
Time (sec)

Figure 2 (facing page). Localizer Scans.

Functional MRI scans obtained from Patient 23 and one healthy control subject are shown. The top sets of scans obtained from the patient (Panel A) and the control subject (Panel B) show activation (yellow and orange) resulting from the motor imagery task (cued with the word "tennis") as compared with rest periods (cued with the word "relax"), as well as the time course of the peak voxel in the supplementary motor area. The bottom sets of scans obtained from the patient (Panel C) and the control subject (Panel D) show activation (blue) resulting from the spatial imagery task (cued with the word "navigation") as compared with rest periods, as well as the time course of the peak voxel in the parahippocampal gyrus. I bars represent standard errors. BOLD denotes blood-oxygenation-level–dependent.

A "Is your father's name Alexander?" "Yes" response with the use of motor imagery

B "Do you have any brothers?" "Yes" response with the use of motor imagery



C "Is your father's name Thomas?" "No" response with the use of spatial imagery

D "Do you have any sisters?" "No" response with the use of spatial imagery

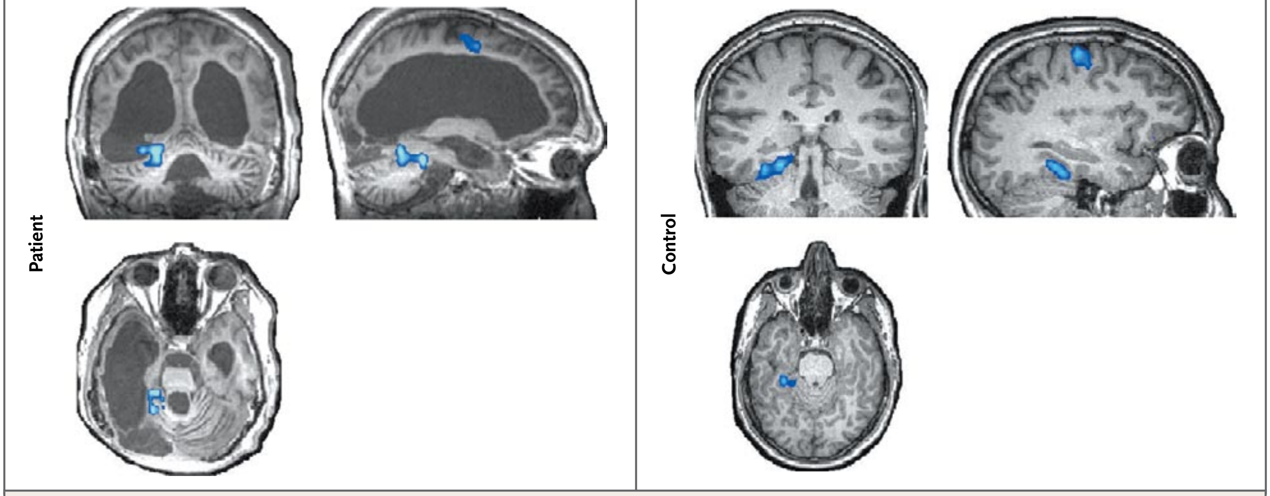


Figure 3. Communication Scans.

Results of two sample communication scans obtained from Patient 23 (Panels A and C) and a healthy control subject (Panels B and D) during functional MRI are shown. In Panels A and B, the observed activity pattern (orange) was very similar to that observed in the motor-imagery localizer scan (i.e., activity in the supplementary motor area alone), indicating a "yes" response. In Panels C and D, the observed activity pattern (blue) was very similar to that observed in the spatial-imagery localizer scan (i.e., activity in both the parahippocampal gyrus and the supplementary motor area), indicating a "no" response. In Panels A and C, the names used in the questions have been changed to protect the privacy of the patient.

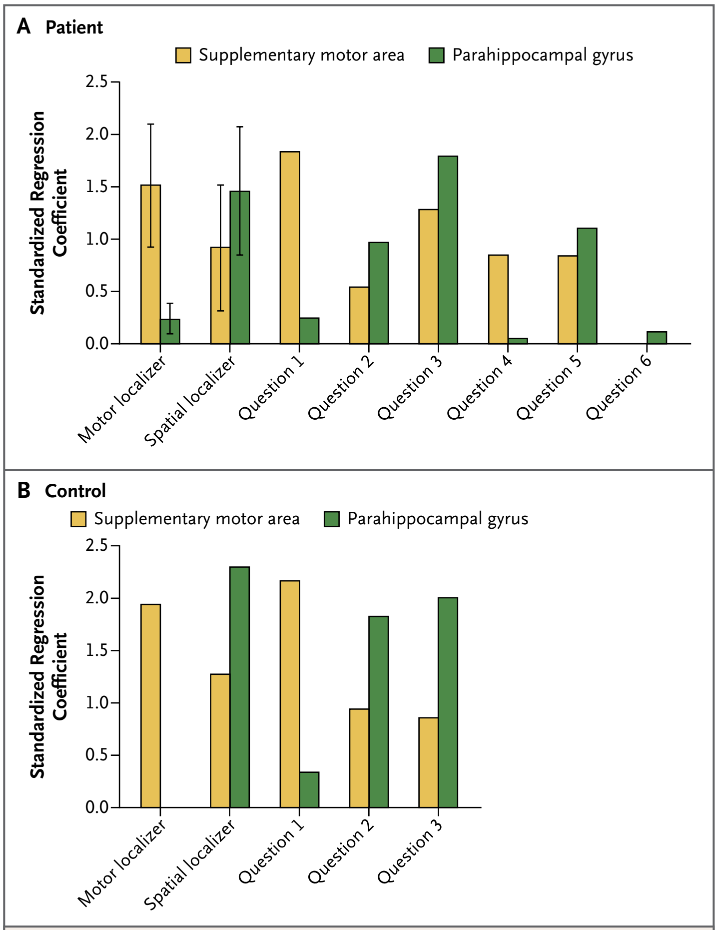


Figure 4. Region-of-Interest Data.

The patterns of activation in the regions of interest (the supplementary motor area and the parahippocampal gyrus) in the motor and spatial localizer scans and the communication scans obtained from one patient and one healthy control subject are shown. The patient was asked to respond to six questions, and the healthy control subject was asked to respond to three questions. The I bars represent standard errors.

a vegetative state was entirely accurate in the sense that no behavioral markers of awareness were evident. That said, the diagnosis did not accurately reflect the patient's internal state of awareness and level of cognitive functioning at the time. Given that all previous assessments were based on behavioral observations alone, these two possibilities are indistinguishable.

Among 49 of the 54 patients included in this study, no significant functional MRI changes were observed during the imagery tasks. In these patients, it is not possible to determine whether the negative findings were the result of the low "sensitivity" of the method (e.g., failure to detect small effects), or whether they genuinely reflect the patients' limited cognitive abilities. Some patients, for example, may have been unconscious (permanently or transiently) during scanning. Similarly, in some awake and aware patients who were in a minimally conscious state, the tasks may simply have exceeded their residual cognitive capabilities. Deficits in language comprehension, working memory, decision making, or executive function would have prevented successful completion of the imagery tasks. However, positive results, whether observed with or without corroborative behavioral data, do confirm that all such processes were intact and that the patient must have been aware.

In summary, the results of this study show the potential for functional MRI to bridge the dissociation that can occur between behavior that is readily observable during a standardized clinical assessment and the actual level of residual cognitive function after serious brain injury.[14-16] Thus, among 23 patients who received a diagnosis of being in a vegetative state on admission, 4 were shown to be able to willfully modulate their brain activity through mental imagery; this fact is inconsistent with the behavioral diagnosis. In two of these patients, however, subsequent assessment at the bedside revealed some behavioral evidence of awareness, a finding that underscores the importance of thorough clinical examination for reducing the rate of misdiagnosis in such patients. Nonetheless, in the two remaining patients, no evidence of awareness could be detected at the bedside by an experienced clinical team, even after the results of the functional MRI examination were known. This finding indicates that, in some patients, motor function can be so impaired that bedside assessments based on the presence or absence of a behavioral response may not reveal awareness, regardless of how thoroughly and carefully they are administered. In patients without a behavioral response, it is clear that functional MRI complements existing diagnostic tools by providing a method for detecting covert signs of residual cognitive function[17-20] and awareness.[10]

In addition, this study showed that in one patient with severe impairment of consciousness, functional MRI established the patient's ability to communicate solely by modulating brain activity, whereas this ability could not be established at the bedside. In the future, this approach could be used to address important clinical questions. For example, patients could be asked if they are feeling any pain, and this information could be useful in determining whether analgesic agents should be administered. With further development, this technique could be used by some patients to express their thoughts, control their environment, and increase their quality of life.

Supported by grants from the Medical Research Council (U.1055.01.002.00007.01 and U.1055.01.002.00001.01), the European Commission (Disorders and Coherence of the Embodied Self, Mindbridge, Deployment of Brain–Computer Interfaces for the Detection of Consciousness in Nonresponsive Patients, and Consciousness: A Transdisciplinary, Integrated Approach), Fonds de la Recherche Scientifique, the James S. McDonnell Foundation, the Mind Science Foundation, the Reine Elisabeth Medical Foundation, the Belgian French-Speaking Community Concerted Research Action, University Hospital of Liege, the University of Liege, and the National Institute for Health Research Biomedical Research Centre (Neurosciences Theme).

No potential conflict of interest relevant to this article was reported.

We thank Daniel Gary Wakeman for his helpful discussions.

REFERENCES

1. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet 1972;1:734-7.

2. Jennett B. The vegetative state: medical aspects, ethical and legal dilemmas. Cambridge, England: Cambridge University Press, 2002.

3. Laureys S. The neural correlate of (un) awareness: lessons from the vegetative state. Trends Cogn Sci 2005;9:556-9.

4. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. N Engl J Med 1994;330:1499-508, 1572-9.

5. The vegetative state: guidance on diagnosis and management. London: Royal College of Physicians of London, 2003.

6. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002; 58:349-53.

7. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 1996;313:13-6.

8. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993;43:1465-7.

9. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9:35.

10. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006;313:1402.

11. Boly M, Coleman MR, Hampshire A, et al. When thoughts become action: an fMRI paradigm to study volatile brain activity in non-communicative brain injured patients. Neuroimage 2007;36:979-92.

12. Weiskopf N, Mathiak K, Bock SW, et al. Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). IEEE Trans Biomed Eng 2004;51:966-70.

13. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23: Suppl 1:S208-S219.

14. Owen AM, Coleman MR. Functional neuroimaging of the vegetative state. Nat Rev Neurosci 2008;9:235-43.

15. Monti MM, Coleman MR, Owen AM. Neuroimaging and the vegetative state: resolving the behavioral assessment dilemma? Ann N Y Acad Sci 2009;1157: 81-9.

16. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3: 537-46.

17. Coleman MR, Rodd JM, Davis MH, et al. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain 2007;130:2494-507.

18. Monti MM, Coleman MR, Owen AM. Executive functions in the absence of behavior: functional imaging of the minimally conscious state. Prog Brain Res 2009;177:249-60.

19. Schnakers C, Perrin F, Schabus M, et al. Voluntary brain processing in disorders of consciousness. Neurology 2008;71: 1614-20.

20. Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17:732-41.

Copyright © 2010 Massachusetts Medical Society.

DISORDERS OF CONSCIOUSNESS: MOVING FROM PASSIVE TO RESTING STATE AND ACTIVE PARADIGMS

Bruno MA.[1*], Soddu A.[1*], Demertzi A.[1], Laureys S.[1,2], Gosseries O.[1], Schnakers C. [1], Boly M. [1], Noirhomme Q.[1], Thonnard M. [1], Chatelle C.[1], Vanhaudenhuyse A.[1]

[1] Coma Science Group, Cyclotron Research Center, University and University Hospital of Liège, Sart-Tilman B30, Liège, Belgium

[2] Department of Neurology, University Hospital of Liège, Sart-Tilman, Liège, Belgium

For Peer Review Only

[*]Bruno MA and Soddu A equally contributed to the manuscript.

Corresponding authors:

Steven Laureys and Audrey Vanhaudenhuyse

Coma Science Group

Cyclotron Research Center

University and University Hospital of Liège

Sart-Tilman B30

Liège, Belgium

steven.laureys@ulg.ac.be and avanhaudenhuyse@student.ulg.ac.be

Tel: +32 4 366 23 16

Fax: +32 4 366 29 46

Acknowledgments

SL is Senior Research Associate; AS, MB and QN are Post-doctoral Fellows and MAB is Research Fellow at the Fonds de la Recherche Scientifique (FRS). This research was supported by the Fonds de la Recherche Scientifique (FRS), the European Commission (DISCOS, Mindbridge, DECODER & CATIA), the Concerted Research Action (ARC-06/11-340), the McDonnell Foundation, Mind Science Foundation.

For Peer Review Only

Abstract

Following coma, some patients will recover wakefulness without sign of consciousness (i.e., vegetative state) or may show non-reflexive movements but with no ability for functional communication (i.e., minimally conscious state). Currently, there remains a high rate of misdiagnosis of the vegetative state. The increasing use of fMRI and EEG tools permits to improve the clinical characterization of these patients. We first discuss “resting metabolism” and “passive activation” paradigms, used in neuroimaging and evoked potential studies, which merely identify neural activation reflecting “automatic” processing – that is, occurring without the patients' willful intervention. Secondly, we present an alternative approach consisting of instructing subjects to imagine well-defined sensory-motor or cognitive-mental actions. This strategy reflects volitional neural activation and, hence, witnesses awareness. Finally, we present results on BOLD “default mode network” studies imply that resting state measurements might be a promising tool in the diagnosis of these challenging patients.

For Peer Review Only

Introduction

Following severe brain damage, patients classically evolve through clinical stages before recovering consciousness. Coma is usually a transient condition which will last no longer than a few days or weeks and is defined as an “unarousable unresponsiveness” (Posner, Saper, Schiff and Plum, 2007). After some days or weeks, comatose patients may open their eyes. When this return to “wakefulness” is accompanied by reflexive motor activity only, the condition is called vegetative state (VS – The Multi-Society Task Force on PVS, 1994). Many patients in VS regain consciousness in the first month after brain injury. If patients show no sign of awareness one year after a traumatic brain injury or three months after an anoxia, the chances of recovery functional communication are considered close to zero and the patient is considered in a permanent VS (The Multi-Society Task Force on PVS, 1994). Those who recover typically progress to a minimally conscious state (MCS), which is characterized by minimal but definite behavioral evidence of awareness of self and/or the environment (Giacino et al., 2002). Like the VS, the MCS may be chronic and sometimes permanent. However, at present, no time-windows for “permanent MCS” have been agreed upon. Reliable and consistent interactive communication and/or functional use of objects indicate the next boundary in the course of recovery – emergence from MCS – (Giacino et al., 2002). Finally, patients may awaken from their coma fully aware but unable to move or speak – the only way they have to express their consciousness is by small eye movements. This state is called the locked-in syndrome (LIS) and is characterized by quadriplegia and anarthria with general preservation of cognition (Schnakers et al., 2008a) and a primary and elementary mode of communication that uses vertical or lateral eye movements (American Congress of Rehabilitation Medicine, 1995).

Behavioral assessment is one of the main methods used to detect awareness in severely brain injured patients recovering from coma (Majerus, Gill-Thwaites, Andrews and

For Peer Review Only

Laureys, 2005). Clinical practice shows that recognizing unambiguous signs of conscious perception in such patients can be very challenging. Indeed, behavioral assessment is complicated by the presence of motor/language impairment, tracheotomy, fluctuating arousal level or ambiguous and rapidly habituating responses (Gill-Thwaites, 2006), which may partly explain the high frequency of misdiagnosis (up to 43%) in these patients (Andrews, Murphy, Munday and Littlewood, 1996; Childs and Mercer, 1996; Schnakers et al., 2009b). This underestimation of the patient's level of consciousness can also be explained by other factors such as poor expertise in behavioral assessment or the use of insensitive behavioral assessment tools (e.g., using a mirror when evaluating visual pursuit, behavior that is considered as one of the first clinical signs differentiating MCS from VS – Vanhaudenhuyse, Schnakers, Bredart and Laureys, 2008b). LIS may also be misdiagnosed as being in a coma or VS (Bruno et al., 2009). This misdiagnosis can be explained by the rarity of this syndrome; by the difficulty of recognizing unambiguous signs of consciousness (i.e., voluntary eye movements or blinking - Majerus, Gill-Thwaites, Andrews and Laureys, 2005); by a fluctuation of vigilance in the acute setting; or by additional cognitive (Schnakers et al., 2008a) or sensory deficits, such as deafness (Bruno et al., 2009; Smart et al., 2008; Keane 1985). Misdiagnosis can lead to grave consequences, especially in end-of-life decision-making (Andrews, 2004). Contrary to patients in VS, those in MCS retain some capacity for cognitive processing (see next section). Moreover, the prognosis of MCS patients is significantly more favorable relative to those in VS (Giacino, 2004a). End-of-life decisions, therefore, are likely to be influenced by whether one is diagnosed with VS or MCS. New technical methods offer specific assessment procedures and the possibility to determine objectively whether an unresponsive patient is aware without explicit verbal or motor response. We here propose to review neuroimaging studies using positron emission tomography, functional magnetic resonance imaging and electrophysiological techniques of

For Peer Review Only

assessment of patients with disorders of consciousness, and present new data on resting state in VS state patients.

Global resting metabolism

Using positron emission tomography (PET), Levy et al. (1987) first showed that patients in a VS suffer from a massive cerebral metabolic reduction, estimated to be 40-50% of normal values. These results have been repeatedly confirmed by others (De Volder et al., 1990; Laureys et al., 1999a; Rudolf, Ghaemi, Haupt, Szelies and Heiss, 1999; Tommasino, Grana, Lucignani, Torri and Fazio, 1995) in VS of different etiologies and duration. In patients with a LIS, overall supratentorial cerebral metabolism has been shown to be preserved partially (Levy et al., 1987) or fully (Laureys, Berré and Goldman, 2001), whereas in comatose patients a decrease of 45% in cerebral metabolism has been observed (Laureys et al., 2001; Tommasino, 1994). However, a global depression of cerebral metabolism is not specific to VS or coma only. In slow wave sleep, overall brain metabolism also decreases approximately to 40% of normal waking values while in REM-sleep metabolism returns to normal values (Maquet et al., 1990). Another example of transient metabolic depression is observed during general anesthesia which is characterized by comparable reduction in cortical metabolism to that observed in VS (Alkire et al., 1995, 1997, 1999). However, we have shown that the relationship between global levels of brain function and the presence or absence of awareness is not absolute; rather, some areas in the brain seem more important than other for the emergence of awareness (Laureys, Faymonville, Moonen, Luxen and Maquet, 2000c; Laureys et al., 1999a). Indeed, VS patients who subsequently recovered consciousness did not show substantial changes in global metabolic rates for glucose metabolism (Laureys, Lemaire, Maquet, Phillips and Franck, 1999b), and some awake healthy volunteers have global brain metabolism values comparable to those observed in some

For Peer Review Only

patients in a VS (Laureys, 2005). In VS, a dysfunction was found not in the all brain but in a wide frontoparietal network encompassing polymodal associative cortices: bilateral lateral frontal regions, parieto-temporal and posterior parietal areas, mesiofrontal, posterior cingulated and precuneal cortices (Laureys et al., 1999a, 2004a). Posterior cingulate and adjacent precuneal cortices were reported to differentiate MCS from VS patients (Laureys, Owen and Schiff, 2004a - intermediate metabolism in MCS, higher than in VS, but lower than in conscious controls). More recently, a study on patients in the chronic stage of traumatic diffuse brain injury showed a bilateral hypometabolism in the medial prefrontal regions, the medial frontobasal regions, the cingulate gyrus and the thalamus. These regions were more hypometabolic in VS than MCS patients, but MCS still showed less activation than patients who have emerged from their MCS and who recovered the ability to communicate (Nakayama, Okumura, Shinoda, Nakashima and Iwama, 2006). Specifically, awareness seems not exclusively related to the activity in the frontoparietal network but, as importantly, to the functional connectivity within this network and the thalami. Indeed, long-range cortico-cortical and cortico-thalamo-cortical “functional disconnections” could be identified in the VS (Laureys et al., 1999a, 2000b).

Passive paradigms: cerebral activation from external stimulation

Functional neuroimaging. Somatosensory, auditory, and visual perceptions are conscious experiences; thus, the wakeful unconsciousness of VS patients, by definition, precludes these experiences. However, the absence of a behavioral response cannot be taken as an absolute proof of the absence of consciousness (Bernat, 1992; McQuillen, 1991). Several functional magnetic resonance imaging (fMRI) activation studies in VS (Bekinschtein et al., 2005; Coleman, et al., 2007; 2009; Di, et al., 2007; Fernandez-Espejo et al., 2008; Moritz et al., 2001; Staffen, Kronbichler, Aichhorn, Mair and Ladurner, 2006) have confirmed previous

For Peer Review Only

PET studies showing preserved activation of “lower level” primary sensory cortices which are disconnected from “higher order” associative cortical networks employing both auditory (Boly et al., 2004; 2005; Laureys et al., 2000a; Owen et al., 2002), somatosensory (Boly et al., 2005; 2008a), or visual (Menon et al., 1998; Owen et al., 2002) stimulations. Similar studies in PET reported that MCS patients showed a more widespread activation than VS, with a cortico-cortical functional connectivity more efficient in MCS compared to VS (Boly et al., 2004). These results confirmed that MCS patients may experience pain and hence should systematically receive appropriate analgesic treatment. Moreover, stimuli with emotional valence (baby cries and own name) were shown to induce a much more widespread activation than did meaningless noise in the MCS (Laureys et al., 2004b). Stimuli with emotional valence (the voice of the patient's mother compared with an unfamiliar voice) were also shown to activate amygdala in a traumatic MCS patient (Bekinschtein et al., 2004). Similarly, Schiff et al. (2005), in two MCS patients, showed selective activation in components of the cortical language networks during presentation of narratives read by a familiar voice and containing personally meaningful content. Such context-dependent higher-order auditory processing shows that content does matter when talking to MCS patients. Finally, some exceptional VS patients may also show higher atypical level of cortical activation in response to auditory stimulations and this was proposed to be a surrogate marker of good prognosis (Di et al., 2007).

For Peer Review Only

Event-related potentials. Event-related potentials (ERPs) have been used for a long time to assess comatose patients. Early components of these potentials arising within 100 milliseconds are known to persist even in unconscious states. The later components of exogenous potentials and other so-called “endogenous” ERP components (e.g., P300) are more reliably related to the (unconscious or conscious) cognitive processing of the information, and less frequently observed in disorders of consciousness (Kotchoubey, 2005; Vanhaudenhuyse, Laureys and Perrin, 2008a). In several studies, ERPs were used to evaluate the integrity of detection of non-communicative patients' own name, in order to assess the possible preservation of residual linguistic and self-processing in these patients. Differential P300 wave to the own name (as compared to other names) was observed in LIS patients (Perrin et al., 2006), which is not surprising since their cognitive functions and their linguistic comprehension remain preserved (Onofrj, Thomas, Paci, Scesi and Tombari, 1997; Schnakers et al., 2008a). In MCS, results suggested that the auditory system was relatively preserved in response to passive tones and language stimulation, implying that these patients are able to detect salient words (Perrin et al., 2006). Most surprisingly, some VS patients emitted a differential P300, although delayed as compared to age-matched controls (Perrin et al., 2006). These last results showed that the P300 wave resulting from a passive paradigm is not useful to successfully disentangle unconscious from conscious patients. However, in most studies, the presence of a P300 correlated with favorable outcome in comatose patients (Vanhaudenhuyse et al., 2008a).

Active paradigms: command following in non-communicative patients

Functional neuroimaging. In the absence of a full understanding of the neural correlates of consciousness, even a near-to-normal activation in response to passive stimulations cannot be considered as a proof of the presence of awareness. Instead, all that can be inferred is that a specific brain region is, to some degree, still able to perceive and process relevant sensory stimuli. The question that arises is how we can disentangle automatic from voluntary conscious brain activation. In 2006, Owen et al. have addressed this concern by applying an fMRI paradigm in a traumatic VS patient which was asked to perform two mental imagery tasks ("Imagine playing tennis" and "Imaging your visiting house"). Activation was observed

For Peer Review Only

in the supplementary motor area after being asked to imagine playing tennis, and in parahippocampal gyrus when asked to imagine visiting her house. Similar activation patterns were seen in healthy volunteers (Boly et al., 2007a). Importantly, because the only difference between the conditions that elicited task-specific activation was in the instruction given at the beginning of each scanning session, the activation observed can only reflect the intentions of the patient, rather than some altered property of the outside world. Some could argue that the words "tennis" and "house" may have automatically triggered the patterns of activation observed in target brain areas in this patient in the absence of conscious awareness. Although it is well documented that these words elicit wholly automatic neural responses in the absence of conscious awareness (Hauk, Johnsrude and Pulvermuller, 2004), such responses typically last for a few seconds and occur in regions of the brain that are associated with word processing. In this patient, the observed activity persisted for the full 30 seconds of each imagery task and persisted until the patient was cued with another stimulus indicating that she should rest. Such responses are, thus, impossible to explain in terms of automatic brain processes (Soddu et al., 2009). In addition, the responses in the patient were observed, not in brain regions that are known to be involved in word processing but, rather, in regions that are known to be involved in the two imagery tasks that she was asked to carry out (Owen et al., 2007). In this sense, the decision to "imagine playing tennis" rather than simply "rest" is an act of willed intention and, therefore, clear evidence for response to command, awareness. The results of this study should not be misinterpreted as evidence that all patients in VS may be conscious. Interestingly, when re-examined six months later, the patient showed inconsistent signs of consciousness. The most likely explanation of these results is that the patient was already beginning the transition to the MCS at the time of the experiment. This study also highlights the importance of fMRI as a potentially good marker for both diagnosis and prognosis (Di et al., 2007).

For Peer Review Only

ERPs. The use of passive ERP paradigm is not sufficient to reliably disentangle VS from MCS. Indeed, even if passive ERP paradigms are able to highlight ongoing brain processing for a given stimulus input, they do not differentiate between automatic and voluntary cognitive processes and, therefore, between unconscious and conscious patients. For this reason, an ERPs active paradigm was developed, where the participant is instructed to voluntarily direct attention to a target stimulus and to ignore other stimuli (Figure 1) (Schnakers et al., 2008b, 2009a). Group as well as individual results showed that a larger P300 response to the own name was observed in MCS patients in active condition as compared to passive listening. This P300 amplitude was otherwise equivalent to that observed in controls, while no task-related P300 changes in VS patients were observed (Schnakers et al., 2008b). This suggests that MCS patients were able to voluntary focus their attention on the target as a function of task requirements. In a last study, this active ERPs paradigm permitted to detect consciousness in a total LIS patient (i.e., characterized by complete immobility including all eye movements – Bauer, Gerstenbrand and Rumpl, 1979), that behaviorally would be diagnosed as comatose (Schnakers et al., 2009a).

FIGURE 1

Resting state fMRI paradigm: a new tool to categorize disorders of consciousness patients?

Resting state fMRI acquisitions are easy to perform and could have a potentially broader and faster translation into clinical practice. Recent studies on spontaneous fluctuations in the functional MRI blood oxygen level-dependent (BOLD) signal recorded in “resting” awake healthy subjects showed the presence of coherent fluctuations among

For Peer Review Only

functionally defined neuro-anatomical networks (Boly et al., 2008b; Raichle, 2006). The concept of a “default mode network” describes a set of brain areas exhibiting task-induced deactivations, encompassing precuneus, posterior parietal lobe and medial prefrontal cortex which are more active at rest than when we are involved in attention-demanding cognitive tasks (Raichle et al., 2001). The clinical interest of default network MRI studies is that it allows the investigation of higher order cognitive networks, without requiring patients’ active participation, particularly important in VS and MCS. We here compared default mode network in VS and brain dead patients with healthy volunteers.

Patients. We first created a healthy control template of the Default Mode (DM) by analyzing 11 volunteers (age range 21-60 years; 4 women). Secondly, we compared 4 brain injured patients (3 vegetative – 1 ischemia, 1 encephalopathy, 1 traumatic – and 1 hemorrhagic brain dead (published in Boly et al., 2009) patients, age range 27-77 years, all men) to 9 other healthy volunteers (age range 29-65 years, 5 women). In patients, clinical examination was repeatedly performed using standardized scales (the Coma Recovery Scale Revised - Giacino et al., 2004b; and the Glasgow Liege scale - Born, 1988) on the day of scanning, and in the week before and the week after. Patients were scanned in an unsedated condition. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate to the study was obtained from the subjects themselves in the case of healthy subjects, and from the legal surrogate of the patients.

Data acquisition and analysis. In all participants, resting state BOLD data were acquired on a 1.5 T MR scanner (Symphony Tim, Siemens, Germany) with a gradient echo-planar sequence using axial slice orientation (36slices; voxel size=3.75x3.75x3.6 mm^3; matrix size=64x64x36; repetition time=3000ms; echo time=30ms; flip angle=90^o ; field of view=240mm). A protocol of 200 scans with a duration of 10 minutes was performed. fMRI

For Peer Review Only

data were preprocessed using the ‘‘BrainVoyager’’ software (R. Goebel, Brain Innovation, Masstricht, The Netherlands). Preprocessing of functional scans included 3D motion correction, linear trend removal, slice scan time correction and filtering out of low frequencies of up to 0.005Hz. The data were spatially smoothed with a Gaussian filter of full width of half maximum value of 8mm. Independent component Analysis (ICA – Formisano et al., 2004) was performed with BrainVoyager using thirty components (Ylipaavalniemi and Vigario, 2008). An average – template – DM map was calculated on 11 healthy subjects. We performed, as implemented in Brain Voyager (self-organizing ICA – Esposito et al., 2005), a spatial similarity test on single subjects independent components (IC) and we averaged the maps belonging to the cluster which was selected by visual inspection as DM. In order to select the DM for each subject and patients, we run self-organizing ICA with the average IC from the template (spatial similarity test). Self-organizing ICA could select an IC as DM and assign a similarity value that indicates how well the selected IC fitted the average DM map based on the template. The same protocol of 200 scans was acquired on a spherical phantom. Finally, a two tails unequal variance Student T-test compared the spatial similarity values of the selected DM map to the average DM based on the template in healthy controls compared to VS patients. Three motion indices were introduced describing the motion of patients compared to healthy controls: the mean frequency calculated as the mean of the frequency of each motion curve (3 translations and 3 rotations), the mean over time of the full displacement during the acquisition calculated as the square root of the sum of the squares of the 6 motion parameters, and the mean over time of the displacement speed during the acquisition calculated as the square root of the sum of the squares of the 6 motion parameters variation over one time unit (repetition time).

Results. Healthy controls mean spatial map identified the DM pattern (Figure 2a) showing full overlap with the template identified by the black and white contour. The

For Peer Review Only

principal brain regions characterizing the DM, posterior cingulate/precuneal, mesiofrontal and posterior parietal cortices, were detected. Compared to controls, VS patients showed a significant lower spatial similarity (0.47±0.08, range 0.33-0.55 *vs.* 0.23±0.12, range 0.12-0.35; p=0.05). The brain dead patient (and the phantom) showed also lower spatial similarity compared to controls with values in the VS range. Finally, none of the VS patients showed a DM with a spatial pattern comparable with healthy controls (Figure 2b-d), as assessed by visual inspection, even if in the case of V1 the spatial similarity had a value consistent with healthy subjects (Table). Rapid transient "clonic" motions were observed for VS1 and VS3 as also confirmed by spatial maps periphery patterns. The brain dead patient didn't show any significant spatial pattern confirming result in Boly et al., 2009.

Discussion. After creating a template of the default mode network (DMn), we identified the DMn at the single subject level, in a user-independent manner. In healthy volunteers, the identified component showed the typical spatial pattern of the DM (Beckmann et al., 2005). In VS patients, as well as in the brain dead, we failed to show any consistent pattern of DMn, even if single subjects brain activation maps showed residual connectivity in VS. In our view, these residual connectivity patterns are not reflecting residual DMn neuronal activity but could be explained by movement artifacts. Cardiorespiratory effects could be also a source of connectivity. BOLD signal changes within regions of the DMn have been found to be reduced after correcting for cardiorespiratory effects (van Buuren et al., 2009; Shmueli et al., 2007; Birn et al., 2006). However, in the absence of simultaneous recording of heart and respiratory rates during the fMRI acquisitions, this remains speculative.This of course cannot exclude the absence of neural activity in these patients (Boly et al., 2009; van Buuren et al., 2009). Boly and collaborators (2009) showed that correlations with posterior cingulate cortex are reduced in one VS as compared to age-matched controls, and argued that these reduced functional connectivity within the DMn in VS was in line with the hypothesis that

For Peer Review Only

spontaneous fMRI signal changes may be partly related to ongoing interoceptive state-of-minds or conscious thoughts. Motion, pulse and respiratory artefacts remain a very important problem to tackle to be able to properly assess patients with disorder of consciousness. If recording heart and respiratory rates during the acquisition can help disentangling neuronal activity from pulse and respiratory artefacts (Gray et al., 2009), further investigations are needed to disentangle effect of motion and neuronal activity in the BOLD signal. Finally, in the brain dead patient, who fulfilled all the standard clinical criteria for brain death (previously published in Boly et al., 2009), fMRI results did not show any long-range significant functional connectivity confirming that the origin of the BOLD signal was fully due to motion artifacts as expected due to the complete absence of neuronal activity in brain death.

For Peer Review Only

FIGURE 2

Conclusion

Patients with disorders of consciousness represent a major clinical problem in terms of clinical assessment, treatment and daily management. The non-responsiveness of such patients implies that they can only be diagnosed by means of exclusion criteria like “no goal-directed eye movements” or “no execution of commands”. Those behavioral signs may be very discrete, short-termed and the performance may be fluctuating. Integration of neuroimaging and ERPs techniques should improve our ability to disentangle diagnostic and prognostic differences on the basis of underlying mechanisms and better guide our clinical therapeutic options in these challenging patients. A step-by-step approach combining multimodal assessment techniques (i.e., PET-scan, fMRI and ERPs) seems to be appropriate to detect signs of consciousness (Figure 3). Resting metabolism and passive paradigms studies increased our understanding of residual cerebral processing of VS and MSC patients. Active paradigm seems to provide an objective valuable additional diagnostic tool in cases of patients with atypical activation, leading to persisting doubts in clinical diagnosis. Negative results, however, must be cautiously interpreted in case of patients with severely altered level of vigilance, which could present only transient activity in response to the presentation of instructions. Passive and active fMRI paradigms were also showed to potentially be a useful tool to predict possibility of recovery. Finally, results on the DMn seem promising to distinguish disorders of consciousness patients by evaluating preservation of connectivity in this resting state network. However, future studies are needed to give a full characterization of default mode connectivity in VS and MCS patients and its potential use in outcome prediction. Future clinical studies should also perform heart rate and respiratory rate recording and simultaneous real movement monitoring which would improve default mode analyses.

FIGURE 3

For Peer Review Only

References

Alkire, M.T., Haier, R.J., Barker, S.J., Shah, N.K., Wu, J.C. and Kao, Y.J. (1995). 'Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography.' Anesthesiology, 82 (2):393-403.

Alkire, M.T., Haier, R.J., Shah, N.K. and Anderson, C.T. (1997). 'Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia'. Anesthesiology, 86 (3):549-557.

Alkire, M.T., Pomfrett, C.J., Haier, R.J., Gianzero, M.V., Chan, C.M., Jacobsen, B.P. and Fallon, J.H. (1999). 'Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism'. Anesthesiology, 90 (3):701-709.

American Congress of Rehabilitation Medicine (1995). 'Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness'. Arch Phys Med Rehabil, 76:205-209.

Andrews, K. (2004). 'Medical decision making in the vegetative state: withdrawal of nutrition and hydration'. NeuroRehabilitation, 19 (4):299-304.

Andrews, K., Murphy, L., Munday, R. and Littlewood, C. (1996). 'Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit'. BMJ, 313 (7048):13-16.

Bauer, G., Gerstenbrand, F. and Rumpl, E. (1979). 'Varieties of the locked-in syndrome'. J Neurol, 221 (2):77-91.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., (2005). Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360, 1001-1013.

For Peer Review Only

Bekinschtein, T., Niklison, J., Sigman, L., Manes, F., Leiguarda, R., Armony, J., Owen, A., Carpintiero, S. and Olmos, L. (2004). 'Emotion processing in the minimally conscious state'. J Neurol Neurosurg Psychiatry, 75 (5):788.

Bekinschtein, T., Tiberti, C., Niklison, J., Tamashiro, M., Carpintiero, S., Villarreal, M., Forcato, C., Leiguarda, R. and Manes, F. (2005). 'Assessing level of consciousness and cognitive changes from vegetative state to full recovery'. Neuropsychological Rehabilitation, 15 (3/4):307-322.

Bernat, J.L. (1992). 'The boundaries of the persistent vegetative state'. J Clin Ethics, 3 (3):176-180.

Birn RM, Diamond JB, Smith MA, Bandettini PA. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31(4):1536-48.

Boly, M., Coleman, M.R., Davis, M.H., Hampshire, A., Bor, D., Moonen, G., Maquet, P.A., Pickard, J.D., Laureys, S. and Owen, A.M. (2007a). 'When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients'. Neuroimage, 36 (3):979-992.

Boly, M., Faymonville, M.E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A., Lamy, M., Moonen, G., Maquet, P. and Laureys, S. (2005). 'Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS'. Neuropsychol Rehabil, 15 (3-4):283-289.

Boly, M., Faymonville, M.E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., Degueldre, C., Franck, G., Luxen, A., Lamy, M., Moonen, G., Maquet, P. and Laureys, S. (2004). 'Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state'. Archives of neurology, 61 (2):233-238.

For Peer Review Only

Boly, M., Faymonville, M.E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., Lancellotti, P., Luxen, A., Lamy, M., Moonen, G., Maquet, P. and Laureys, S. (2008a). 'Perception of pain in the minimally conscious state with PET activation: an observational study'. Lancet Neurol.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T.T., Moonen, G., Maquet, P. and Laureys, S. (2008b). 'Intrinsic brain activity in altered states of consciousness. How conscious is the default mode of brain function?' Annals of the New York Academy of Sciences, 1129:119-129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., Boveroux, P., Garweg, C., Lambermont, B., Phillips, C., Luxen, A., Moonen, G., Bassetti, C., Maquet, P. and Laureys, S. (2009). 'Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient'. Hum Brain Mapp, 30 (8):2393-2400.

Born JD. 1988. The Glasgow-Liège Scale. Prognostic value and evaluation of motor response and brain stem reflexes after severe head injury. Acta Neurochir 95:49-52.

Bruno, M.A., Schnakers, C., Damas, F., Pellas, F., Lutte, I., Bernheim, J., Majerus, S., Moonen, G., Goldman, S. and Laureys, S. (2009). 'Locked-in syndrome in children: report of five cases and review of the literature'. Pediatr Neurol, 41 (4):237-246.

Childs, N.L. and Mercer, W.N. (1996). 'Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs [letter; comment]'. BMJ, 313 (7062):944.

Coleman, M.R., Davis, M.H., Rodd, J.M., Robson, T., Ali, A., Owen, A.M. and Pickard, J.D. (2009). 'Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness'. Brain, 132 (Pt 9):2541-2552.

For Peer Review Only

Coleman, M.R., Rodd, J.M., Davis, M.H., Johnsrude, I.S., Menon, D.K., Pickard, J.D. and Owen, A.M. (2007). 'Do vegetative patients retain aspects of language comprehension? Evidence from fMRI'. Brain, 130 (10):2494-2507.

De Volder, A.G., Goffinet, A.M., Bol, A., Michel, C., de, B.T. and Laterre, C. (1990). 'Brain glucose metabolism in postanoxic syndrome. Positron emission tomographic study.' Arch. Neurol., 47 (2):197-204.

Di, H.B., Yu, S.M., Weng, X.C., Laureys, S., Yu, D., Li, J.Q., Qin, P.M., Zhu, Y.H., Zhang, S.Z. and Chen, Y.Z. (2007). 'Cerebral response to patient's own name in the vegetative and minimally conscious states'. Neurology, 68 (12):895-899.

Esposito, F., Scarabino, T., Hyvarinen, A., Himberg, J., Formisano, E., Comani, S., Tedeschi, G., Goebel, R., Seifritz, E., Di Salle, F., (2005). Independent component analysis of fMRI group studies by self-organizing clustering. Neuroimage 25, 193-205.

Fernandez-Espejo, D., Junque, C., Vendrell, P., Bernabeu, M., Roig, T., Bargallo, N. and Mercader, J.M. (2008). 'Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury'. Brain Inj, 22 (11):882-890.

Formisano, E., Esposito, F., Di Salle, F., Goebel, R., (2004). Cortex-based independent component analysis of fMRI time series. Magn Reson Imaging 22, 1493-1504.

Giacino, J.T. (2004a). 'The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis'. NeuroRehabilitation, 19 (4):293-298.

Giacino JT, Kalmar K, Whyte J. (2004b). The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85(12):2020-9.

Giacino, J.T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D.I., Kelly, J.P., Rosenberg, J.H., Whyte, J., Zafonte, R.D. and Zasler, N.D. (2002). 'The minimally conscious state: Definition and diagnostic criteria'. Neurology, 58 (3):349-353.

For Peer Review Only

Gill-Thwaites, H. (2006). 'Lotteries, loopholes and luck: misdiagnosis in the vegetative state patient'. Brain Inj, 20 (13-14):1321-1328.

Gray, M.A., Minati, L., Harrison, N.A., Gianaros, P.J., Napadow, V., Critchley, H.D., (2009). Physiological recordings: basic concepts and implementation during functional magnetic resonance imaging. Neuroimage 47, 1105-1115.

Hauk, O., Johnsrude, I. and Pulvermuller, F. (2004). 'Somatotopic representation of action words in human motor and premotor cortex'. Neuron, 41 (2):301-307.

Keane, J.R. (1985). 'Locked-in syndrome with deafness'. Neurology, 35 (9):1395.

Kotchoubey, B., (2005). 'Event-related potential measures of consciousness: two equations with three unknown'. In: Laureys, S. (ed). The boundaries of consciousness: neurobiology and neuropathology. Amsterdam: Elsevier, 427-444.

Laureys, S. (2005). 'The neural correlate of (un)awareness: lessons from the vegetative state'. Trends Cogn Sci, 9 (12):556-559.

Laureys, S., Berré, J. and Goldman, S., (2001). 'Cerebral function in coma, vegetative state, minimally conscious state, locked-in syndrome and brain death'. In: Vincent, J.L. (ed). 2001 Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 386-396.

Laureys, S., Faymonville, M.E., Degueldre, C., Fiore, G.D., Damas, P., Lambermont, B., Janssens, N., Aerts, J., Franck, G., Luxen, A., Moonen, G., Lamy, M. and Maquet, P. (2000a). 'Auditory processing in the vegetative state'. Brain, 123 (8):1589-1601.

Laureys, S., Faymonville, M.E., Luxen, A., Lamy, M., Franck, G. and Maquet, P. (2000b). 'Restoration of thalamocortical connectivity after recovery from persistent vegetative state'. Lancet, 355 (9217):1790-1791.

Laureys, S., Faymonville, M.E., Moonen, G., Luxen, A. and Maquet, P. (2000c). 'PET scanning and neuronal loss in acute vegetative state'. Lancet, 355:1825-1826.

For Peer Review Only

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., Franck, G. and Maquet, P. (1999a). 'Impaired effective cortical connectivity in vegetative state'. Neuroimage, 9 (4):377-382.

Laureys, S., Lemaire, C., Maquet, P., Phillips, C. and Franck, G. (1999b). 'Cerebral metabolism during vegetative state and after recovery to consciousness'. J Neurol Neurosurg Psychiatry, 67 (1):121.

Laureys, S., Owen, A.M. and Schiff, N.D. (2004a). 'Brain function in coma, vegetative state, and related disorders'. Lancet Neurol, 3 (9):537-546.

Laureys, S., Perrin, F., Faymonville, M.E., Schnakers, C., Boly, M., Bartsch, V., Majerus, S., Moonen, G. and Maquet, P. (2004b). 'Cerebral processing in the minimally conscious state'. Neurology, 63 (5):916-918.

Levy, D.E., Sidtis, J.J., Rottenberg, D.A., Jarden, J.O., Strother, S.C., Dhawan, V., Ginos, J.Z., Tramo, M.J., Evans, A.C. and Plum, F. (1987). 'Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients'. Ann Neurol, 22 (6):673-682.

Majerus, S., Gill-Thwaites, H., Andrews, K. and Laureys, S.l. (2005). 'Behavioral evaluation of consciousness in severe brain damage'. Prog Brain Res, 150:397-413.

Maquet, P., Dive, D., Salmon, E., Sadzot, B., Franco, G., Poirrier, R., von, Frenckell, R. and Franck, G. (1990). 'Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method.' Brain Res., 513 (1):136-143.

McQuillen, M.P. (1991). 'Can people who are unconscious or in the "vegetative state" perceive pain?' Issues Law Med., 6 (4):373-383.

Menon, D.K., Owen, A.M., Williams, E.J., Minhas, P.S., Allen, C.M., Boniface, S.J. and Pickard, J.D. (1998). 'Cortical processing in persistent vegetative state.' Lancet, 352 (9123):200.

For Peer Review Only

Moritz, C.H., Rowley, H.A., Haughton, V.M., Swartz, K.R., Jones, J. and Badie, B. (2001). 'Functional MR imaging assessment of a non-responsive brain injured patient'. Magnetic Resonance Imaging, 19 (8):1129-1132.

Nakayama, N., Okumura, A., Shinoda, J., Nakashima, T. and Iwama, T. (2006). '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, 77 (7):856-862.

Onofrj, M., Thomas, A., Paci, C., Scesi, M. and Tombari, R. (1997). 'Event related potentials recorded in patients with locked-in syndrome'. J Neurol Neurosurg Psychiatry, 63 (6):759-764.

Owen, A., Coleman, M., Boly, M., Davis, M., Laureys, S., Jolles, J. and Pickard, J. (2007). 'Response to Comments on "Detecting Awareness in the Vegetative State"'. Science, 315 (5816).

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S. and Pickard, J.D. (2006). 'Detecting awareness in the vegetative state'. Science, 313 (5792):1402.

Owen, A.M., Menon, D.K., Johnsrude, I.S., Bor, D., Scott, S.K., Manly, T., Williams, E.J., Mummery, C. and Pickard, J.D. (2002). 'Detecting residual cognitive function in persistent vegetative state'. Neurocase, 8 (5):394-403.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., Faymonville, M.E., Lamy, M., Moonen, G., Luxen, A., Maquet, P. and Laureys, S. (2006). 'Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome'. Arch Neurol, 63 (4):562-569.

Posner, J., Saper, C., Schiff, N. and Plum, F., (2007). Plum and Posner's diagnosis of stupor and coma. New York: Oxford University Press.

For Peer Review Only

Raichle, M.E. (2006). 'Neuroscience. The brain's dark energy'. Science, 314 (5803):1249-1250.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. and Shulman, G.L. (2001). 'A default mode of brain function'. Proc Natl Acad Sci U S A, 98 (2):676-682.

Rudolf, J., Ghaemi, M., Haupt, W.F., Szelies, B. and Heiss, W.D. (1999). 'Cerebral glucose metabolism in acute and persistent vegetative state'. Journal of neurosurgical anesthesiology, 11 (1):17-24.

Schiff, N.D., Rodriguez-Moreno, D., Kamal, A., Kim, K.H., Giacino, J.T., Plum, F. and Hirsch, J. (2005). 'fMRI reveals large-scale network activation in minimally conscious patients'. Neurology, 64 (3):514-523.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., Pellas, F., Bartsch, V., Peigneux, P., Moonen, G. and Laureys, S. (2008a). 'Cognitive function in the locked-in syndrome'. J Neurol, 255 (3):323-330.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., Boly, M., Vanhaudenhuyse, A., Bruno, M.A. and Laureys, S. (2009a). 'Detecting consciousness in a total locked-in syndrome: An active event-related paradigm'. Neurocase:1-7.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., Boly, M., Vanhaudenhuyse, A., Bruno, M.A., Moonen, G. and Laureys, S. (2008b). 'Voluntary brain processing in disorders of consciousness'. Neurology, 71:1614-1620.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., Moonen, G. and Laureys, S. (2009b). 'Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment'. BMC Neurol, 9:35.

For Peer Review Only

Shmueli K, van Gelderen P, de Zwart JA, Horovitz SG, Fukunaga M, Jansma JM, Duyn JH. (2007). Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. Neuroimage 38(2):306-20.

Smart, C.M., Giacino, J.T., Cullen, T., Moreno, D.R., Hirsch, J., Schiff, N.D. and Gizzi, M. (2008). 'A case of locked-in syndrome complicated by central deafness'. Nat Clin Pract Neurol, 4 (8):448-453.

Soddu A, Boly M, Nir Y, Noirhomme Q, Vanhaudenhuyse A, Demertzi A, Arzi A, Ovadia S, Stanziano M, Papa M and others. (2009). Reaching across the abyss: recent advances in functional magnetic resonance imaging and their potential relevance to disorders of consciousness. Prog Brain Res 177:261-74.

Staffen, W., Kronbichler, M., Aichhorn, M., Mair, A. and Ladurner, G. (2006). 'Selective brain activity in response to one's own name in the persistent vegetative state'. J Neurol Neurosurg Psychiatry, 77 (12):1383-1384.

The Multi-Society Task Force on PVS (1994). 'Medical aspects of the persistent vegetative state (1).' N Engl J Med, 330 (21):1499-1508.

Tommasino, C. (1994). 'Brain glucose metabolism in the comatose state and in post-comatose syndromes.' Minerva Anestesiol., 60 (10):523-525.

Tommasino, C., Grana, C., Lucignani, G., Torri, G. and Fazio, F. (1995). 'Regional cerebral metabolism of glucose in comatose and vegetative state patients.' J. Neurosurg. Anesthesiol., 7 (2):109-116.

van Buuren M, Gladwin TE, Zandbelt BB, van den Heuvel M, Ramsey NF, Kahn RS, Vink M. (2009). Cardiorespiratory effects on default-mode network activity as measured with fMRI. Hum Brain Mapp 30(9):3031-42.

Vanhaudenhuyse, A., Laureys, S. and Perrin, F. (2008a). 'Cognitive event-related potentials in comatose and post-comatose states'. Neurocrit Care, 8 (2):262-270.

For Peer Review Only

Vanhaudenhuyse, A., Schnakers, C., Bredart, S. and Laureys, S. (2008b). 'Assessment of visual pursuit in post-comatose states: use a mirror'. J Neurol Neurosurg Psychiatry, 79 (2):223.

Ylipaavalniemi, J., Vigario, R., (2008). Analyzing consistency of independent components: an fMRI illustration. Neuroimage 39, 169-180.

For Peer Review Only

Figures Legend

Figure 1: Illustration of active and passive event-related potential paradigms in a 22 year-old locked in syndrome patient. Upper panels depict the patient's response to an unfamiliar name (listened non-target unfamiliar name, in blue) as compared with active condition (counted target unfamiliar name, in red). Lower panel depict the patient's own name response in the passive condition (listened non-target own name, in green) and in the active condition (counted target own name, in pink). (Adapted from data published by Schnakers, et al., 2009a)

Figure 2: Resting state EPI-BOLD acquisition in**: a.** 9 healthy volunteers, with a spatial map obtained by running a random effect group GLM analysis using as predictors the time courses of the ICs selected as default mode (thresholded at false discovery rate corrected $p<0.05$) within default mode mask obtained from an independent dataset (the 11 healthy controls for the independent study) shown as black and white contour volume of interest. **b-d.** 3 vegetative patients and 1 brain death with spatial maps obtained by running a GLM analysis using as predictor the time courses of the ICs selected as default mode (thresholded at false discovery rate corrected $p<0.05$).

Figure 3: Illustration of a step-by-step approach combining PET scan, ERPs and fMRI techniques which might reveal signs of consciousness that are unattainable by bedside clinical assessment of disorders of consciousness patients. These high-tech devices might permit some of these patients to show their consciousness by following commands (e.g., "imaging playing tennis", "count your own name") via non-motor pathways. ERPs: event-related potentials; fMRI: functional MRI.

For Peer Review Only

Table

Spatial and temporal properties of the independent component selected as default mode (DM) from resting state fMRI in healthy controls, vegetative (VS) and one brain death (BD) patients (Phantom is added for comparison): spatial similarity with an average – template – default mode based on an independent 11 healthy controls data set, normalized variation of spatial similarity (Sim) respect to the brain death (BD) (Sim_subject-Sim_BD)/Sim_BD), and default mode time course mean frequency. Motion properties (means calculated from the six motion curves). Rapid transient "clonic" motions were observed for two of the three patients (VS1 and VS3) as also confirmed by spatial maps periphery patterns, while a drift (i.e. a displacement with low speed.) is observed for control 3 and 7.

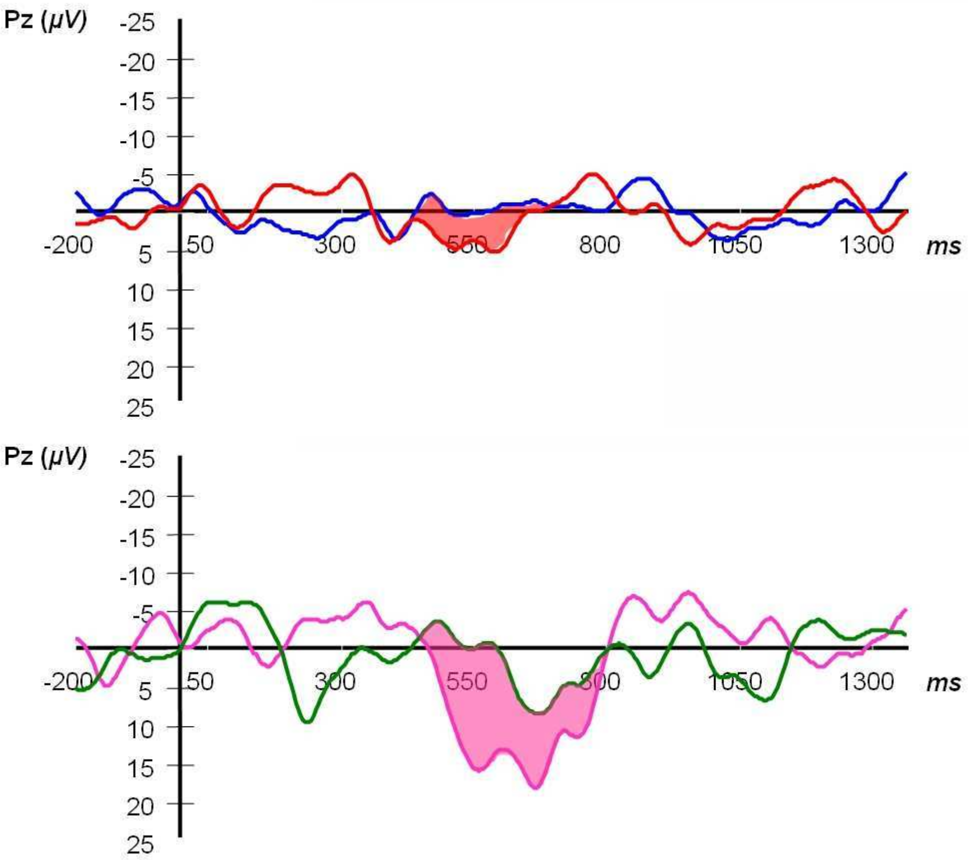
	Spatial Similarity	**Normalized variation of Spatial Similarity**	**DM Time Course Mean Frequency (Hz)**	**Motion Curves Mean Frequency (Hz)**	**Mean Displacement**	**Mean Speed**
Control 1	0.33	1.5	0.04	0.03	0.6	0.04
Control 2	0.51	2.9	0.05	0.06	0.3	0.14
Control 3	0.37	1.8	0.05	0.03	1.7	0.09
Control 4	0.50	2.8	0.05	0.06	0.4	0.14
Control 5	0.54	3,2	0.07	0.05	0.8	0.25
Control 6	0.39	2	0.04	0.04	0.3	0.02

For Peer Review Only

Control 7	0.55	3.2	0.05	0.03	3.0	0.09
Control 8	0.54	3.2	0.05	0.04	0.3	0.03
Control 9	0.47	2.6	0.04	0.03	0.8	0.05
VS 1	0.35	1.7	0.04	0.05	1.1	0.14
VS 2	0.23	0.8	0.07	0.05	0.2	0.28
VS 3	0.12	-0.1	0.04	0.03	5.9	0.50
BD	0.13	0	0.07	0.06	0.1	0.27
Phantom	0.12	-0.1	0.06	0.03	0.1	0.24

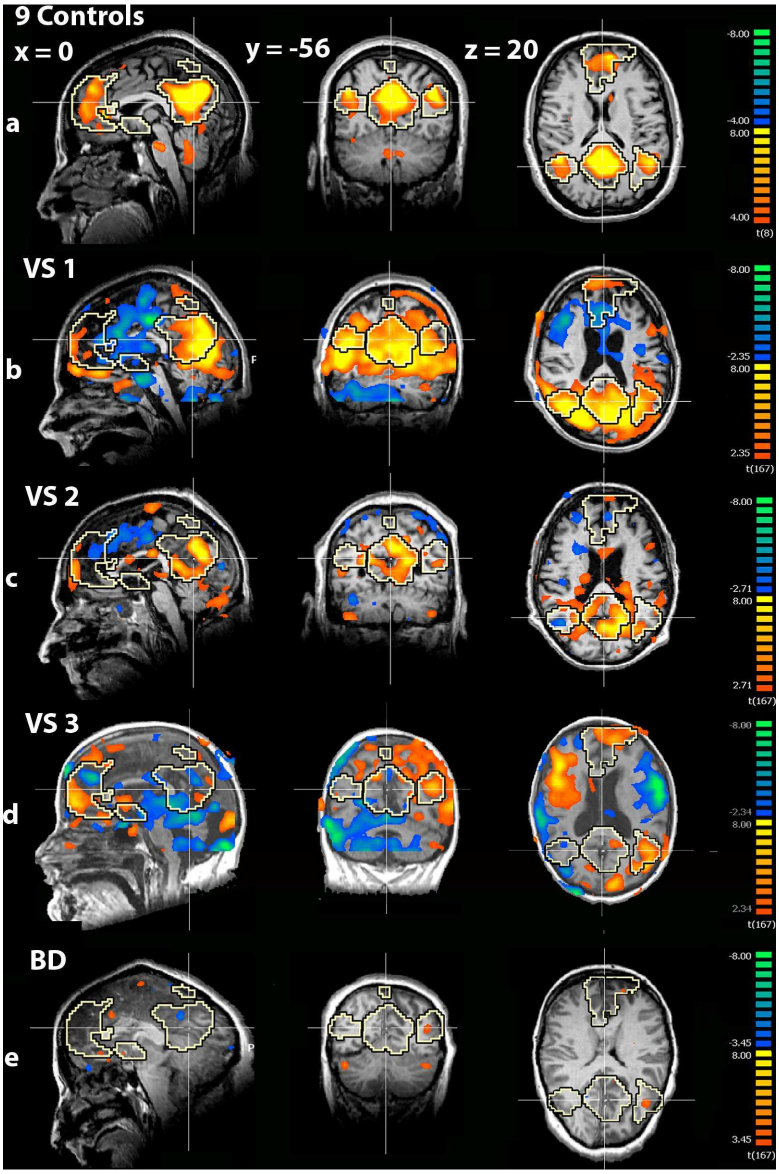
For Peer Review Only

For Peer Review Only

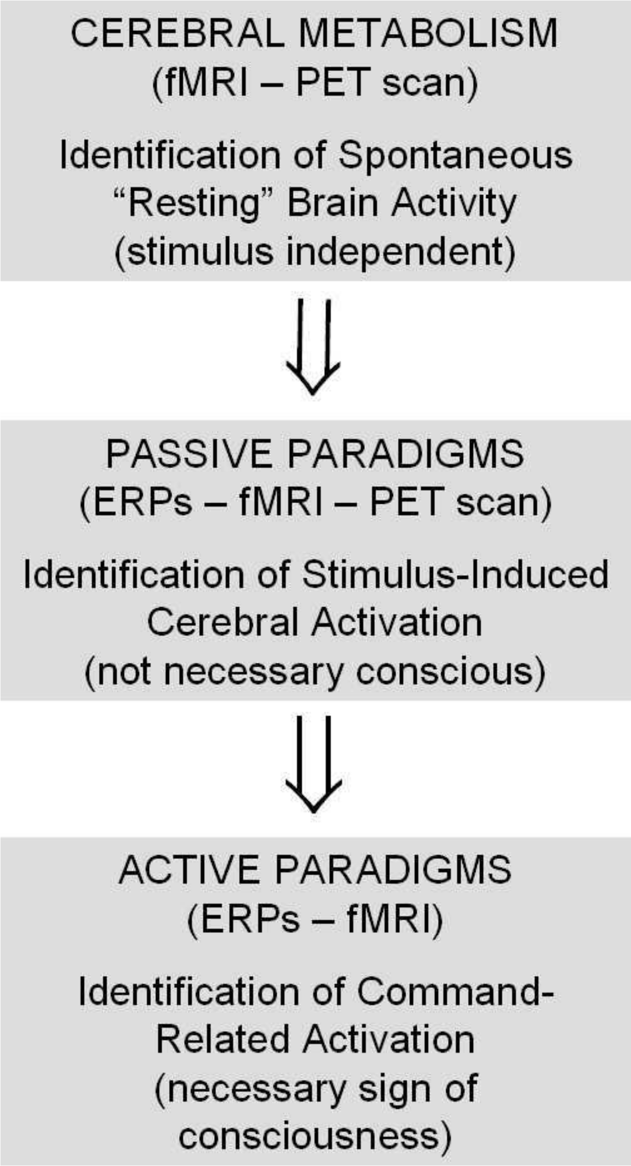


41x36mm (600 x 600 DPI)

Only



68x102mm (600 x 600 DPI)



21x39mm (600 x 600 DPI)

the specific letters that were briefly presented to them, they do have cognitive access to the fact that they were presented with an array of 12 characters. Their cognitive access is limited, but so too may be their phenomenal consciousness of those letters. If one holds a "movie screen of the mind" model of phenomenal consciousness, it may seem impossible that there could be letters that are phenomenally present as letters without being present as specific letter shapes. But such a model is at best problematic, and if one rejects it, then there seems no reason why the characters of which the subjects are aware could not be indeterminate in ways that exactly match their limited cognitive access to those features.

Moreover, the subjects' reports of what they experienced under such marginal conditions may be more problematic than Block contends. He rejects the idea that they might be hyperillusions – cases in which how it seems that it seems, is not how it really seems. He says he knows of no such illusions. However, the well-known color marker demonstration (Dennett 1991) would seem to be just that. We have the firm belief that our phenomenal experience of the entire visual field is colored; that is how it seems to us. But if we hold fixation to the front and hold a marker whose color we do not know at arms length to the side, we cannot discern its color. If it is gradually moved toward the front, we cannot see its color until it is far toward the center of our field of vision, though we can detect its motion almost as soon as it begins to move – which reflects the fact that the retina lacks cones at the periphery but not motion detectors. Nor is the illusion easily dispelled, as Block says is generally true of cognitive illusions. Despite participating in the marker demonstration, one still experiences the illusion (hyperillusion) that one's whole visual field is phenomenally colored.

The possibility that phenomenal consciousness may admit of degrees also enlarges the space of alternatives against which Block's view must be compared in assessing his IBE argument. He contrasts his position mainly with what he calls metaphysical and epistemological correlationism, but these views, like his own, do not consider the possibility that phenomenal consciousness may be partial, indeterminate, and admitting of degrees. If one allows for that possibility, then there are other hypotheses one might consider about whether cognitive access is sometimes a constitutive element of phenomenal consciousness.

If the neural substrate of phenomenal consciousness involves interactions among multiple brain regions, and the specific regions vary for different experiences – two ideas Block endorses in general – then could it not be the case that sometimes those regions most active in providing cognitive access are among the relevant constitutive elements? The suggestion is not merely hypothetical. As Block acknowledges, phenomenal consciousness involves some sort of awareness. Indeed, it involves the awareness or experience of objects present to the self – that is, objects experienced from the perspective of the self. There need not involve a commitment to any traditional substantial notion of the self. The self and the self-perspective may well be virtual structures. As I look at my desk the phenomenal content of my experience is that a blue mug is present here and now before me. In light of the integrative role played by the machinery of cognitive access, it seems plausible to regard it as constituting part of the substrate of my phenomenal consciousness of that mug as an object in my world, rather than merely a cause of my experience.

Perhaps in marginal and attenuated cases, we may have phenomenal experiences of isolated properties or features, and in such cases perhaps all the constitutive elements of our phenomenal consciousness lie outside the structures that support cognitive access. But those would be cases in which we are phenomenally conscious to a lesser degree than is typical. In more normal cases of full-blown phenomenal consciousness, we experience colors, shapes, and motions as properties of objects present to us as part of our world. And in those cases, it seems plausible to treat the regions that present those objects to us, that give us access to those objects, as parts of the substrate of such phenomenal consciousness.

The challenge of disentangling reportability and phenomenal consciousness in post-comatose states

doi: 10.1017/S0140525X0700310X

Audrey Vanhaudenhuyse[a], Marie-Aurélie Bruno[a], Serge Brédart[b], Alain Plenevaux [c], and Steven Laureys[a]
[a]*Coma Science Group, Cyclotron Research Center, University of Liège, Sart Tilman B30, 4000 Liège, Belgium;* [b]*Department of Cognitive Science, University of Liège, Sart Tilman B32, 4000 Liège, Belgium;* [c]*Department of Cognitive Sciences, Cyclotron Research Center, University of Liège, Sart Tilman B30, 4000 Liège, Belgium.*
avanhaudenhuyse@student.ulg.ac.be www.comascience.org
marieaureliebruno@hotmail.com www.comascience.org
serge.bredart@ulg.ac.be http://www.fapse.ulg.ac.be/Lab/Cog/
alain.plenevaux@ulg.ac.be http://www.ulg.ac.be/crc/index.html
steven.laureys@ulg.ac.be www.comascience.org

Abstract: Determining whether or not noncommunicative patients are phenomenally conscious is a major clinical and ethical challenge. Clinical assessment is usually limited to the observation of these patients' motor responses. Recent neuroimaging technology and brain computer interfaces help clinicians to assess whether patients are conscious or not, and to avoid diagnostic errors.

Block differentiates phenomenal consciousness and its cognitive access based on empirical data obtained with healthy subjects and neglect syndrome patients. Evidencing consciousness in noncommunicative patients is an important theoretical, medical, and ethical issue. In this commentary, we first emphasize the problem faced when determining the presence of phenomenal consciousness in vegetative and minimally conscious states in absence of any verbal response; second, we show that phenomenal consciousness may occur without verbal or motor reports in patients with a complete locked-in syndrome.

Vegetative state (VS) is characterized by "wakefulness without consciousness," accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment (The Multi-Society Task Force on PVS 1994). Minimally conscious state (MCS) describes patients who are unable to communicate while demonstrating inconsistent but reproducible behavioral evidence of consciousness. Patients in MCS may show command-following, gestural or verbal yes/no response, intelligible speech, and purposeful behavior (Giacino et al. 2002). Neurological practice illustrates how difficult it is to identify signs of conscious perception in such patients. Misdiagnosis of VS occurs in about one-third of patients (Andrews et al. 1996; Childs et al. 1993). Consciousness is a subjective experience and by definition VS and MCS patients are noncommunicative; we are therefore limited to observing their motor responses and interpreting them in terms of consciousness. Functional neuroimaging procedures provide an opportunity to find the neural correlates of phenomenal consciousness in these patients.

The problem is that there is no validated objective "consciousness meter" that can be used as a proof or disproof of consciousness in such patients. Passive paradigms such as auditory and pain perception showed that brain activations were significantly different between VS and MCS (for a review, see Giacino et al. 2006). But in the absence of a thorough understanding of the neural correlates of consciousness, brain activations observed with passive paradigms are not sufficient to know whether or not these patients are phenomenally conscious. Brain activations observed by using passive paradigms could reflect consciousness but they could also simply reflect nonconscious processing (see studies on subliminal priming or nonconscious processing during sleep and anesthesia). Active paradigms may provide a means for detecting phenomenal consciousness in brain-damaged patients (Boly et al. 2007). Owen et al. (2006) have recently used such paradigms by asking patients to actively perform mental imagery tasks. In one exceptional VS patient studied five months after trauma, activation was observed in the supplementary motor area after the patient was asked to imagine playing tennis; and in premotor, parahippocampal, and posterior parietal cortices when asked to imagine visiting her house. Identical activation was observed in healthy volunteers. The aforementioned patient's neural responses by imagining tasks when asked to do so confirmed that she was phenomenally conscious (Boly et al. 2007; Owen et al. 2006; 2007).

We concur with Block when he claims that conscious states would not magically disappear in a person who is unable to report conscious states. In this context we emphasize the complete locked-in syndrome (LIS). Classical LIS is defined by sustained eye opening, aphonia, quadriplegia, vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses, and preserved consciousness (American Congress of Rehabilitation Medicine 1995). Complete LIS consists of total immobility including all eye movements (Bauer et al. 1979). In approximately half of LIS patients the diagnosis initially is missed (Laureys et al. 2005). Julia Tavalaro, a LIS patient whose diagnosis was missed for 6 years, illustrates that phenomenal consciousness can exist for many years in the absence of reportability. Although Tavalaro was actually fully conscious, she was called "the vegetable" – she documents this horrible experience in her book, *Look Up for Yes* (Tavalaro & Tayson 1997). Another testimony comes from an unpublished case we witnessed. This patient was considered as being vegetative for 15 years after a traumatic brain injury, although he was conscious. Now he can talk; and, using a facilitated communication device, he talks of his despair during these years of isolation.

Brain computer interfaces (BCI), also named "thought translation devices," have shown their utility to document consciousness in LIS. BCI is a communication system in which the 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 (Kubler & Neumann 2005). In end-stage amyotrophic lateral sclerosis (ALS), near-complete LIS patients were able to communicate without any verbal or motor report, but were able to do so solely by modulating their EEG (Birbaumer et al. 1999; Hinterberger et al. 2005). BCI can use surface electrodes but is faster when intracortical electrodes are used (Hochberg et al. 2006). Finally, mental manipulation of salivary pH has been used as a form of non-motor mediated communication in one complete LIS ALS patient (Wilhelm et al. 2006). Figure 1 graphically illustrates such "Yes" (imagine lemon)/"No" (imagine milk) communication we obtained from a healthy volunteer.

Bedside evaluation of consciousness in severely brain-damaged patients who cannot verbally or behaviorally report their putative phenomenal consciousness is intrinsically difficult. New functional neuroimaging techniques employing "active" mental imagery paradigms have shown their interest in the assessment of VS and MCS. The rare but horrifying condition of complete LIS illustrates that phenomenal consciousness may remain present for many years in the absence of any overt reportability.

ACKNOWLEDGENTS

Steven Laureys is research associate at the Belgian Fonds National de la Recherche Scientifique (FNRS). Audrey Vanhaudenhuyse is funded by a grant from the French Speaking Community of Belgium (Concerted Research Action 06/11-340).

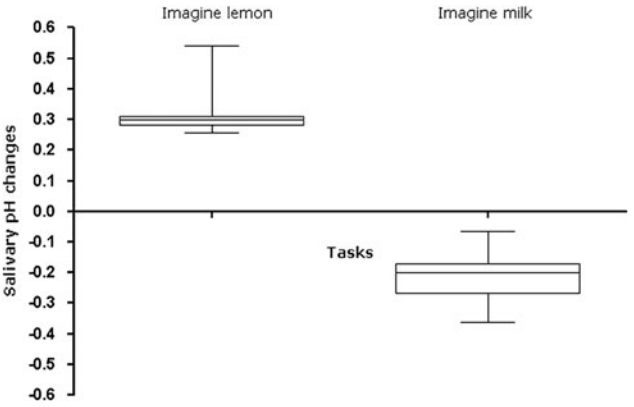


Figure 1 (Vanhaudenhuyse et al.). Nonverbal report of phenomenal consciousness using salivary pH changes. A healthy subject communicated "Yes" (i.e., imagine lemon) or "No" (i.e., imagine milk) while salivary pH changes were monitored (as compared with baseline). Box (mean and standard deviation) and whickers (minima and maxima) obtained during a single untrained session; 2 minutes of imagery for each task.

Author's Response

Overflow, access, and attention

doi: 10.1017/S0140525X07003111

Ned Block
Department of Philosophy, New York University, New York, NY 10003.
ned.block@nyu.edu

Abstract: In this response to 32 commentators, I start by clarifying the overflow argument. I explain why the distinction between generic and specific phenomenology is important and why we are justified in acknowledging specific phenomenology in the overflow experiments. Other issues discussed are the relations among report, cognitive access, and attention; panpsychic disaster; the mesh between psychology and neuroscience; and whether consciousness exists.

R1. Introduction

I have learned a great deal from reading the commentaries and I am gratified that so many respondents are sympathetic to separating phenomenal consciousness from cognitive access to it – a stark contrast to the responses to an earlier BBS paper (Block 1995), in which I argued for similar though slightly stronger views. I don't flatter myself with the supposition that I have convinced anyone – the main factor is that a wide range of accumulating evidence increasingly supports separating phenomenal consciousness and cognitive access. (Evidence beyond what is described in the target article is mentioned in **Gopnik**; **Izard, Quinn, & Most** [**Izard et al.**]; **Koch & Tsuchiya**; **Lamme**; **Landman & Sligte; Malach;** and **Snodgrass & Lepisto**.)

The empirical core of my argument in the target article concerned what I called overflow, that is, that the capacity of the phenomenal system is higher than the capacity of the cognitive access system that underlies reportability of phenomenal states. Many of the respondents (**Burge**;

R7. Does consciousness even exist?

McDermott says that the ultimate theory of how the brain works "will of course not refer to anything like phenomenology, but only to neural structures," concluding that as science marches on, notions of phenomenal consciousness will give way to neurally specified cognitive access. I have two criticisms. First, why *replacement* rather than *reduction*? The distinction I am appealing to is described in every introductory Philosophy of Science text (e.g., Rosenberg 2005). To illustrate: The concept of "phlogiston" has been *replaced* by the concept of oxygen. By contrast, we still have the concepts of heat and temperature. Heat has been *reduced* to molecular kinetic energy: heat exists and is molecular kinetic energy. Reductionist physicalists (a category that includes people as diverse as me and the Churchlands) hold that phenomenal consciousness can be reduced in neuroscientific terms. McDermott speaks of the buzz saw that is cutting through the science of consciousness. But the buzz saw of the revolution in chemistry in the eighteenth century did not show that there was no such thing as heat, temperature, pressure, or entropy, but rather, that they could be understood in molecular terms, that is, reduced rather than replaced. Of course, there are some cases to which the reduction/replacement distinction does not neatly apply. One much discussed example is the gene (Darden & Tabery 2007) for which there is no straightforward answer to the question of whether there are genes and they are snippets of DNA, or whether genes have been shown to not exist. Perhaps the most charitable interpretation of McDermott's remarks on life and subjectivity is that he predicts that the case of consciousness will end up resembling the case of the gene.

My second criticism of **McDermott** is: Why suppose that the reduction or replacement of the future will be in terms of access as opposed to lower-level neuroscience; for example, in terms of recurrent activation of neural connections? Computer scientists tend to assume – without argument – that anything a neuroscientist might discover about what consciousness is will be basically computational. They often assume it will be implementable in a silicon computer. The underlying disagreement here is between physicalist and functionalist reduction (or replacement). The difference is a form of a dispute about the mind/body problem that has been around in one form or another for ages and is discussed in detail in my two most recent books (Block 2007; 2008).

References

[The letters "a" and "r" before author's initials stand for target article and response references, respectively.]

Abrams, R. L. & Grinspan, J. (2007) Unconscious semantic priming in the absence of partial awareness. *Consciousness and Cognition* 16:942–53. [rNB]

Adelson, E. H. (1978) Iconic storage: The role of rods. *Science* 201:544–46. [aNB]

Aimola Davies, A. M. (2004) *Disorders of spatial orientation and awareness: Cognitive and behavioral rehabilitation: From neurobiology to clinical practice.* Guilford Press. [aNB]

Alkire, M. T. & Miller, J. (2005) General anesthesia and the neural correlates of consciousness. *Progress in Brain Research* 150:229–44. [aNB]

Alter, T. & Walter, S. (2006) *Phenomenal concepts and phenomenal knowledge: New essays on consciousness and physicalism*. Oxford University Press. [rNB]

Alvarez, G. A. & Oliva, A. (in press) The representation of ensemble visual features outside the focus of attention. *Psychological Science*. [rNB]

American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Archives of Physical Medicine and Rehabilitation* 76:205–209. [AV]

Anderson, A. K. & Phelps, E. A. (2001) Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 411:305–09. [CEI]

Andrade, J. (2001) The contribution of working memory to conscious experience. In: *Working memory in perspective*, ed. J. Andrade. Psychology Press. [TB]

Andrews, K., Murphy, L., Munday, R. & Littlewood, C. (1996) Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal* 313(7048):13–16. [AV]

Aristotle (1955) On dreams. In: *Aristotle. Parva naturalia*, ed. W. D. Ross, pp. 175–223. Clarendon Press. [aNB]

Armstrong, D. M. (1968) *A materialist theory of the mind*, Humanities Press. [rNB]

(1977) The causal theory of the mind. *Neue Heft für Philosophie* 11:82–95. [aNB]

(1981) What is consciousness? In: *The nature of mind and other essays*, by D. M. Armstrong, pp. 55–67. Cornell University Press. [WGL]

Arnell, K. M., Killman, K. V. & Fijavz, D. (2007) Blinded by emotion: Target misses follow attention capture by arousing distractors in RSVP. *Emotion* 7:465–77. [CEI]

Avidan, G., Hasson, U., Hendler, T., Zohary, E. & Malach, R. (2002) Analysis of the neuronal selectivity underlying low fMRI signals. *Current Biology* 12(12):964–72. [RM]

Baars, B. J. (1988) *A cognitive theory of consciousness.* Cambridge University Press. [KB, aNB]

(1997) *In the theater of consciousness: The workspace of the mind.* Oxford University Press. [KB, aNB, RWK, DM]

(2002) The conscious access hypothesis: Origins and recent evidence. *Trends in Cognitive Sciences* 6(1):47–52. [MSh]

(2005) Global Workspace theory of consciousness: Toward a cognitive neuroscience of human experience. *Progress in Brain Research* 150:45–53. [VAFL]

Baars, B. & Franklin, S. (2003) How conscious experience and working memory interact. *Trends in Cognitive Sciences* 17(4):166–72. [rNB, MSh]

Baars, B. J., Ramsoy, T. Z. & Laureys, S. (2003) Brain, conscious experience and the observing self. *Trends in Neurosciences* 26(12):671–75. [RM]

Bartels, A. & Zeki, S. (2004) Functional brain mapping during free viewing of natural scenes. *Human Brain Mapping* 21. [aNB]

Basso, A., Speinnler, H., Vallar, G. & Zanobio, M. E. (1982) Left hemisphere damage and selective impairment of auditory verbal short term memory: A case study. *Neuropsychologia* 20:263–74. [aNB]

Bauer, G., Gerstenbrand, F. & Rumpl, E. (1979) Varieties of the locked-in syndrome. *Journal of Neurology* 221(2):77–91. [AV]

Bechara, A., Damasio, H. & Damasio, A. (2000) Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex* 10:295–307. [CEI]

Bermúdez, J. & Macpherson, F. (1998) Nonconceptual content and the nature of perceptual experience. *Electronic Journal of Analytical Philosophy* 6 (1998). Archived at: http://ejap.louisiana.edu/archives.html [AC]

Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kubler, A., Perelmouter, J., Taub, E. & Flor, H. (1999) A spelling device for the paralysed. *Nature* 398(6725):297–98. [AV]

Block, N. (1978) Troubles with functionalism. *Minnesota Studies in the Philosophy of Science* 9:261–325. [aNB]

(1980) What is functionalism? In: *Readings in the philosophy of psychology*, ed. N. Block, pp.171–84. Harvard University Press. [aNB]

(1983) The photographic fallacy in the debate about mental imagery. *Nous* 17:651–62. [rNB]

(1990) Consciousness and accessibility. *Behavioral and Brain Sciences* 13(4):596–98. [KB, aNB]

(1992) Begging the question against phenomenal consciousness. *Behavioral and Brain Sciences* 15(2):205–206. [aNB]

(1995a) How many concepts of consciousness? *Behavioral and Brain Sciences* 18(2):272–84. [aNB]

(1995b) On a confusion about a function of consciousness. *Behavioral and Brain Sciences* 18(2):227–47. [KB, arNB, LN, JKO, JP, WGL]

(1997) Biology versus computation in the study of consciousness. *Behavioral and Brain Sciences* 20(1):159–66. [aNB]

(2001) Paradox and cross purposes in recent work on consciousness. *Cognition* 79(1–2):197–220. [arNB, LN]

(2002) Concepts of consciousness. In: *Philosophy of mind: Classical and contemporary readings*, ed. D. Chalmers, pp. 206–18. Oxford University Press. [KB, rNB]

(2003) Mental paint. In: *Reflections and replies: Essays on the philosophy of Tyler Burge*, ed. M. Hahn & B. Ramberg. MIT Press. [PJ]

(2005) Two neural correlates of consciousness. *Trends in Cognitive Sciences* 9(2):46–52. [arNB, VAFL, RL, LN]

(2007) Remarks on chauvinism and the mind-body problem. In: *Consciousness, function, and representation*, vol. 1, ed. N. Block, pp. 7–12. MIT Press. [rNB]

(2007) Wittengstein and qualia. *Philosophical Prespectives* 21(1):73–115. [PJ]

(in press) Functional reduction. In: *Supervenience in mind*, ed. T. Horgan, M. H. Sabates & D. Sosa, MIT Press. [rNB]

Block, N. & Dworkin, G. (1974) IQ, heritability, and inequality I. *Philosophy and Public Affairs* 3(4):331–409. [aNB]

Boghossian, P. A. (2006) *Fear of knowledge: Against relativism and constructivism.* Oxford University Press. [aNB]

Bohm, D. & Hiley, B. J. (1993) *The undivided universe: An ontological interpretation of quantum theory.* Routledge. [DM]

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., Maquet, P. A., Pickard, J. D., Laureys, S. & Owen, A. M. (2007) When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage* 36(3):979–92. [AV]

Breitmeyer, B. G., Kropfl, W. & Julesz, B. (1982) The existence of and role of retinotogic and spatiotopic forms of visual persistence. *Acta Psychologica* 52:175–96. [RL]

Breitmeyer, B. G., Ro, T. & Singhal, N. S. (2004) Unconscious color priming occurs at stimulus- not percept-dependent levels of processing. *Psychological Science* 15(3):198–202. [RL]

Brentano, F. (1874/1924) *Psychologie vom Empirischen Standpunkt.* Felix Meiner. [aNB, DMR]

Britten, K. H., Shadlen, M. N., Newsome, W. T. & Movshon, A. (1992) The analysis of visual motion: A comparison of neuronal and psychophysical performance. *Journal of Neuroscience* 12:4745–65. [aNB]

Brockmole, J. R., Wang, R. F. & Irwin, D. E. (2002) Temporal integration between visual images and visual percepts. *Journal of Experimental Psychology: Human Perception and Performance* 28(2):315–34. [rNB]

Burge, T. (2006) Reflections on two kinds of consciousness. In: *Philosophical essays, vol. II: Foundations of mind*, ed. T. Burge, pp. 392–419. Oxford University Press. [aNB]

Bushnell, I. W. R., Sai, F. & Mullin, J. T. (1989) Neonatal recognition of the mother's face. *British Journal of Developmental Psychology* 7:3–15. [CEI]

Byrne, A. (2004) What phenomenal consciousness is like. In: *Higher order theories of consciousness*, ed. R. Gennaro. John Benjamins. [aNB]

Carrasco, M. (2007) Visual attention alters appearance: Psychophysical studies of subjective experience. In: *Oxford companion to consciousness*, ed. P. Wilken, T. Bayne & A. Cleeremans. Oxford University Press. [aNB]

Carrasco, M., Ling, S. & Read, S. (2004) Attention alters appearance. *Nature Neuroscience* 7(3):308–313. [aNB, RWK]

Carruthers, P. (1989) Brute experience. *Journal of Philosophy* 86:258–69. [rNB]

(1992) *The animals issue: Moral theory in practice.* Cambridge University Press. [rNB]

(1999) Sympathy and subjectivity. *Australasian Journal of Philosophy* 77:465–82. [rNB]

(2000) *Phenomenal consciousness: A naturalistic theory.* Cambridge University Press. [aNB]

Caston, V. (2002) Aristotle on consciousness. *Mind* 111(444):751–815. [arNB]

Cattell, J. M. (1885) The inertia of the eye and brain. *Brain* 8(3):295–312. [aNB]

Cavanagh, P. He, S. & Intriligator, J. (1999) Attentional resolution: The grain and locus of visual awareness. In: *Neuronal basis and psycological aspects of consciousness*, ed. C. Taddai-Ferretti, C. Musio. World Scientific. [rNB]

Chalmers, D. (1996) *The conscious mind: In search of a fundamental theory*. Oxford University Press. [aNB, DM]

(1997) Availability: The cognitive basis of experience. *Behavioral and Brain Sciences* 20(1):148–49. [aNB].

(1998) On the search for the neural correlate of consciousness. In: *Toward a science of consciousness II: The second Tucson discussions and debates*, ed. S. Hameroff, A. Kaszniak & A. Scott, pp. 219–30. MIT Press. [aNB]

(2000) What is a neural correlate of consciousness? In: *Neural correlates of consciousness: Empirical and conceptual issues*, ed. T. Metzinger, pp. 17–40. MIT Press. [aNB]

Childs, N. L., Mercer, W. N. & Childs, H. W. (1993) Accuracy of diagnosis of persistent vegetative state. *Neurology* 43(8):1465–67. [AV]

Chisholm, R. (1942) The problem of the speckled hen. *Mind* 51:368–73. [MSp]

Chun, M. M. & Potter, M. C. (1995) A two-stage model for multiple target detection in rapid serial visual presentation. *Journal of Experimental Psychology: Human Perception and Performance* 21:109–27. [CEI]

Churchland, P. S. (1986) *Neurophilosophy: Toward a unified science of the mind-brain*. MIT Press. [aNB]

(1994) Can neurobioloby teach us anything about consciousness? *American Philosophical Association Proceedings* 67(4):23–40. [aNB]

(2002) *Brain-wise: Studies in neurophilosophy.* MIT Press. [aNB]

(2005) A neurophilosophical slant on consciousness research. *Progress in Brain Research* 149:285–92. [aNB]

Claxton, L. J., Keen, R. & McCarty, M. E. (2003) Evidence of motor planning in infant reaching behavior. *Psychological Science* 14:354–56. [CEI]

Cohen, J. (2002) The grand illusion illusion. *Journal of Consciousness Studies* 9(5–6):141–57. [aNB]

Coltheart, M. (1980) Iconic memory and visible persistence. *Perception and Psychophysics* 27(3):183–228. [AB, aNB]

Cowan, N. (1995) *Attention and memory: An integrated framework.* Oxford University Press. [RL]

(2001) The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences* 24:87–185. [aNB]

(2005) Working-memory capacity limits in a theoretical context. In: *Human learning and memory: Advances in theory and applications*, ed. C. Izawa & N. Ohta, pp. 155–75. Erlbaum. [rNB]

(in press) What are the differences between long-term, short-term, and working memory? In: *The essence of memory*, ed. W. Sossin, J.-C. Jacaille, V. F. Castellucci & S. Belleville. Elsevier/Academic Press. [rNB]

Cowan, N., Morey, C. & Chen, Z. (2007) The legend of the magical number seven. In: *Tall tales about the brain: Things we think we know about the mind, but ain't so*, ed. S. Della Sala, pp. 45–59. Oxford University Press. [aNB]

Cowey, A. & Walsh, V. (2000) Magnetically induced phosphenes in sighted, blind and blindsighted subjects. *NeuroReport* 11:3269–73. [aNB]

Crick, F. & Koch, C. (1995) Are we aware of neural activity in primary visual cortex? *Nature* 375:121–23. [aNB, CK]

(1998a) Consciousness and neuroscience. *Cerebral Cortex* 8:97–107. [CK]

(1998b) Why is there a hierarchy of visual cortical and thalamic areas: The no-strong loops hypothesis. *Nature* 391:245–49. [CK]

(2005) What is the function of the claustrum? *Philosophical Transactions of the Royal Society of London B* 360:1271–319. [CK]

Csikszentmihalyi, M. (1975) *Beyond boredom and anxiety*. Jossey-Bass. [rNB]

(1990) *Flow: The psychology of optimal experience*. Harper and Row. [GH]

Curtis, C. & D'Esposito, M. (2003) Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences* 7(9):415–23. [aNB]

Damasio, A. (1999) *The feeling of what happens: Body and emotion in the making of consciousness.* Harcourt Brace. [aNB]

Darden, L. & Tabery, J. (2007) Molecular biology. In: *The Stanford encyclopedia of philosophy (Fall 2007 edition)*, ed. E. N. Zalta. Online publication. Available at: http://plato.stanford.edu/archives/fall2007/entries/molecular-biology. [rNB]

de Fockert, J. W., Rees, G., Frith, C. D. & Lavie, N. (2001) The role of working memory in visual selective attention. *Science* 291:1803–06. [aNB]

Debner, J. A. & Jacoby, L. L. (1994) Unconscious perception: Attention, awareness, and control. *Journal of Experimental Psychology: Learning, Memory, and Cognition* 20:304–17. [rNB, HL]

Dehaene, S. & Changeux, J. P. (2004) Neural mechanisms for access to consciousness. In: *The cognitive neurosciences III*, ed. M. Gazzaniga, pp. 1145–58. MIT Press. [aNB]

Dehaene, S., Changeux, J.-P., Naccache, L., Sackur, J. & Sergant, C. (2006) Conscious, preconscious, and subliminal processing: A testable taxonomoy. *Trends in Cognitive Sciences* 10(5):204–11. [arNB, AC, SK, RL, VAFL, LN, CS, MSh]

Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J. B., Le Bihan, D. & Cohen, L. (2004) Letter binding and invariant recognition of masked words: Behavioral and neuroimaging evidence. *Psychological Science* 15(5):307–13. [LN]

Dehaene, S., Kerszberg, M. & Changeux, J.-P. (1998) A neuronal model of a global workspace in effortful cognitive tasks. *Proceedings of the National Academy of Sciences USA* 95:14529–34. [aNB, MSh]

Dehaene, S. & Naccache, L. (2001) Towards a cognitive neuroscience of consciousness: Basic evidence and a workspace framework. *Cognition* 79(1–2):1–37. [aNB, LN, JP, DMR]

Dehaene, S., Naccache, L., Le Clec, H. G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., van de Moortele, P. F. & Le Bihan, D. (1998) Imaging unconscious semantic priming. *Nature* 395(6702):597–600. [CS]

Dehaene, S., Sergent, C. & Changeux, J. P. (2003) A neuronal network model linking subjective reports and objective physiological data during conscious perception. *Proceedings of the National Academy of Sciences USA* 100:8520–25. [CS]

Demkiw, P. & Michaels, C. (1976) Motion information in iconic memory. *Acta Psychologica* 40:257–64. [aNB]

Dennett, D. C. (1988) Quining Qualia. In: *Consciousness in contemporary science*, ed. A. Marcel & E. Bisiach, pp. 381–414. Oxford University Press. [aNB]

(1991) *Consciousness explained.* Little, Brown. [arNB, RVG, PJ, CS]

(1993) The message is: There is no medium. *Philosophy and Phenomenological Research* 53(4):889–931. [aNB]

(2001) Are we explaining consciousness yet? *Cognition* 79:221–37. [aNB]

Di Lollo, V. (1980) Temporal integration in visual memory. *Journal of Experimental Psychology: General* 109:75–97. [aNB]

Di Lollo, V., Enns, J. T. & Rensink, R. A. (2000) Competition for consciousness among visual events: The psychophysics of reentrant visual processes. *Journal of Experimental Psychology: General* 129:481–507. [CEI]

Dienes, Z. & Scott, R. (2005) Measuring unconscious knowledge: Distinguishing structural knowledge and judgment knowledge. *Psychological Research* 69(5–6):338–51. [CS]

Dretske, F. (1993) Conscious experience. *Mind* 102(406):263–83. Also published in: Dretske, F. (2000) *Perception, knowledge and belief*. Cambridge University Press. [PJ]

(1994) Differences that make no difference. *Philosophical Topics* 22(1–2):41–57. Also published in: Dretske, F (2000) *Perception, knowledge and belief*. Cambridge University Press. [PJ]

(2004) Change blindness. *Philosophical Studies* 120(1–3):1–18. [aNB]

Driver, J. & Vuilleumier, P. (2001) Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition* 79(1–2):39–88. [aNB, CK]

Edelman, G. M. (2004) *Wider than the sky: The phenomenal gift of consciousness.* Yale University Press. [aNB]

Eimas, P. D. & Quinn, P. C. (1994) Studies on the formation of perceptually based basic-level categories in young infants. *Child Development* 65:903–17. [CEI]

Ellsworth, C. P., Muir, D. W. & Hains, S. M. J. (1993) Social competence and person-object differentiation: An analysis of the still-face effect. *Developmental Psychology* 29:63–73. [CEI]

Engel, G. R. (1970) An investigation of visual responses to brief stereoscopic stimuli. *Quarterly Journal of Experimental Psychology* 22:148–60. [aNB]

Evans, G. (1982) *The Varieties of reference*, ed. J. McDowell. Oxford University Press. [AC]

Fearing, F. (1970) *Reflex action.* MIT Press. [CK]

Feigenson, L. & Carey, S. (2003) Tracking individuals via object files: Evidence from infants' manual search. *Developmental Science* 6:568–84. [arNB]

(2005) On the limits of infants' quantification of small object arrays. *Cognition* 97(3):295–313. [rNB]

Feigenson, L., Carey, S. & Hauser, M. (2002) The representations underlying infants' choice of more: Object files versus analog magnitudes. *Psychological Science* 13:150–56. [arNB]

Fodor, J. A. (1983) *The modularity of mind.* MIT Press. [aNB]

Fuster, J. M. (1973) Unit activity in prefrontal cortex during delayed-response performance: Neuronal correlates of transient memory. *Journal of Neurophysiology* 36:61–78. [aNB]

Gaillard, R., Del Cul, A., Naccache, L., Vinckier, F., Cohen, L. & Dehaene, S. (2006) Nonconscious semantic processing of emotional words modulates conscious access. *Proceedings of the National Academy of Sciences USA* 103(19):7524–29. [CS]

Gazzaniga, M. S., Ivry, R. & Mangun, G. (2002) *Cognitive neuroscience: The biology of the mind.* W. W. Norton. [aNB]

Gazzaniga, M. S., LeDoux, J. E. & Wilson, D. H. (1977) Language, praxis, and the right hemisphere: Clues to some mechanisms of consciousness. *Neurology* 27(12):1144–47. [LN]

Gennaro, R. (1996) *Consciousness and self-consciousness*. John Benjamins. [WGL]

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., Kelly, J. P., Rosenberg, J. H., Whyte, J., Zafonte, R. D. & Zasler, N. D. (2002) The minimally conscious state: Definition and diagnostic criteria. *Neurology* 58(3):349–53. [AV]

Giacino, J. T., Hirsch, J., Schiff, N. & Laureys, S. (2006) Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation* 87(12, Suppl. 2):S67–76. [AV]

Gill, N. F. & Dallenbach, K. M. (1926) A preliminary study of the range of attention. *The American Journal of Psychology* 37(2):247–56. [aNB]

Goldberg, I. I., Harel, M. & Malach, R. (2006) When the brain loses its self: Prefrontal inactivation during sensorimotor processing. *Neuron* 50(2):329–39. [rNB, RM, JP]

Goldman-Rakic, P. (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of physiology: The nervous system, higher functions of the brain*, ed. F. Plum, pp. 373–417. American Physiological Society. [aNB]

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y. U., Hasson & Malach, R. (2007) Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. *Cerebral Cortex* 17(4):766–77. [RM]

Goodale, M. A., Milner, A. D., Jakobson, L. S. & Carey, D. P. (1991) A neurological dissociation between perceiving objects and grasping them. *Nature* 349:154–56. [HL]

Goodman, N., (1976) *Languages of art: An approach to a theory of symbols*, 2nd edition. Hacket Publishing Company. [HL]

Greenwald, A. G., Abrams, R. L., Naccache, L. & Dehaene, S. (2003) Long-term semantic memory versus contextual memory in unconscious number processing. *Journal of Experimental Psychology: Learning, Memory, and Cognition* 29(2):235–47. [CS]

Grill-Spector, K., Sayres, R. & Ress, D. (2006) High-resolution imaging reveals highly selective nonface clusters in the fusiform face area. *Nature Neuroscience* 9:1177–85. [aNB]

(2007) Corrigendum. *Nature Neuroscience* 10:133. [aNB]

Haase, S. & Fisk, G. (2001) Confidence in word detection predicts word identification: Implications for an unconscious perception paradigm. *American Journal of Psychology* 114:439–68. [MSn]

Hanley, J. R., Young, H. W. & Pearson, N. A. (1991) Impairment of visuo-spatial sketch pad. *Quarterly Journal of Experimental Psychology A* 43:101–25. [aNB]

Harman, G. (1965) The inference to the best explanation. *The Philosophical Review* 74(1):88–95. [aNB]

(1990) The intrinsic quality of experience. *Philosophical Perspectives* 4:31–52. [GH]

Harrison, R. V., Harel, N., Panesar, J. & Mount, R. J. (2002) Blood capillary distribution correlates with hemodynamic-based functional imaging in cerebral cortex. *Cerebral Cortex* 12(3):225–33. [CK]

Hasselmo, M. E. & Stern, C. E. (2006) Mechanisms underlying working memory for novel information. *Trends in cognitive sciences* 10(11): 487–93. [aNB]

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G. & Malach, R. (2004) Intersubject synchronization of cortical activity during natural vision. *Science* 303(5664):1634–40. [arNB, RM]

Hauser, M., Carey, S. & Hauser, L. (2000) Spontaneous number representation in semi-free-ranging rhesus monkeys. *Proceedings of the Royal Society of London: Biological Sciences* 267:829–33. [aNB]

Haynes, J. D., Driver, J. & Rees, G. (2005) Visibility reflects dynamic changes of effective connectivity between V1 and fusiform cortex. *Neuron* 46(5): 811–21. [VAFL, LN]

Haynes, J. D. & Rees, G. (2006) Decoding mental states from brain activity in humans. *Nature Reviews Neuroscience* 7(7):523–34. [aNB, LN]

Heath, R. G., Carpenter, M. B., Mettler, F. A. & Kline, N. S. (1949) Visual apparatus: Visual fields and acuity, color vision, autokinesis. In: *Selective partial ablation of the frontal cortex: A correlative study of its effects on human psychotic subjects; problems of the human brain*, ed. F. A. Mettler, pp. 489–91. P. B. Hoeber. [aNB]

Heeger, D. J., Boynton, G. M., Demb, J. B., Seideman, E. & Newsome, W. T. (1999) Motion opponency in visual cortex. *Journal of Neuroscience* 19:7162–74. [aNB]

Heywood, C. A. & Kentridge, R. W. (2003) Achromatopsia, color vision and cortex. *Neurological Clinics of North America* 21:483–500. [RWK]

Heywood, C. A., Kentridge, R. W. & Cowey, A. (1998) Form and motion from colour in cerebral achromatopsia. *Experimental Brain Research* 123:145–53. [RWK]

Hinterberger, T., Birbaumer, N. & Flor, H. (2005) Assessment of cognitive function and communication ability in a completely locked-in patient. *Neurology* 64:1307. [AV]

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Mukand, J. A., Saleh, M., Caplan, A. H., Branner, A., Chen, D., Penn, R. D. & Donoghue, J. P. (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 442(7099):164–71. [AV]

Hofer, H., Singer, B. & Williams, D. R. (2005) Different sensations from cones with the same photopigment. *Journal of Vision* 5:444–54. [RWK]

Hopkin, M. (2006) 'Vegetative' patient shows signs of conscious thought. *Nature* 443(7108):132–33. [aNB]

Huang, L. & Pashler, H. (2007) A Boolean map theory of visual attention. *Psychological Review* 114(3):599–631. [rNB]

Huang, L., Treisman, A. & Pashler, H. (2007) Characterizing the limits of human visual awareness. *Science* 317:823–25. [rNB]

Huk, A. C., Ress, D. & Heeger, D. J. (2001) Neuronal basis of the motion aftereffect reconsidered. *Neuron* 32:161–72. [aNB]

Huntley-Fenner, G., Carey, S. & Solimando, A. (2002) Objects are individuals but stuff doesn't count: Perceived rigidity and cohesiveness influence infants' representations of small numbers of discreet entities. *Cognition* 85:203–21. [aNB]

Hupe, J. M., James, A. C., Payne, B. R., Lomber, S. G., Girard, P. & Bullier, J. (1998) Cortical feedback improves discrimination between figure and background by V1, V2, and V3 neurons. *Nature* 394(6695):784–87. [RL]

Hurley, S. L. (1997) Non-conceptual self-consciousness and agency: Perspective and access. *Communication and Cognition* 30(3/4):207–48. (Part 1 of Special Issue: *Approaching Consciousness*). [AC]

Iwasaki, S. (1993) Spatial attention and two modes of visual consciousness. *Cognition* 49:211–33. [CK]

Izard, C. E. (in press) Basic emotions, natural kinds, emotion schemas, and a new paradigm. *Perspectives on Psychological Science*. [CEI]

Izard, C. E., Fantauzzo, C. A., Castle, J. M., Haynes, O. M., Rayias, M. F. & Putnam, P. H. (1995) The ontogeny and significance of infants' facial expressions in the first 9 months of life. *Developmental Psychology* 31:997–1013. [CEI]

Jackson, F. & Pinkerton, R. J. (1973) On an argument against sensory items. *Mind* 82:269–72. [MSp]

James, T. W., Culham, J., Humphre, G. K., Milner, A. D. & Goodale, M. A. (2003) Ventral occipital lesions impair object recognition but not object-directed grasping: An fMRI study. *Brain* 126:2463–75. [CEI]

James, W. (1890) *Principles of psychology.* Henry Holt. [aNB]

Jiang, Y., Costello, P., Fang, F., Huang, M. & He, S. (2006) A gender- and sexual orientation-dependent spatial attentional effect of invisible images. *Proceedings of the National Academy of Sciences USA* 103:17048–52. [rNB, CEI]

Jolij, J. & Lamme, V. A. F. (2005) Repression of unconscious information by conscious processing: Evidence from affective blindsight induced by transcranial magnetic stimulation. *Proceedings of the National Academy of Sciences USA* 102(30):10747–51. [RL]

Kamitani, Y. & Tong, F. (2005) Decoding the visual and subjective contents of the human brain. *Nature Neuroscience* 8:679–85. [aNB]

Kammer, T. (1999) Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: Their topographic relationship. *Neuropsychologia* 37:191–98. [aNB]

Kanwisher, N. (2001) Neural events and perceptual awareness. *Cognition* 79:89–113. [aNB]

(2006) What's in a face? *Science* 311(5761):617–18. [aNB]

(2007) Does the fusiform face area contain subregions highly selective for nonfaces? *Nature Neuroscience* 10(1):3–4. [aNB]

Kastner, S., De Weerd, P., Desimone, R. & Ungerleider, L. G. (1998) Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* 282(5386):108–11. [LN]

Kentridge, R. W., Heywood, C. A. & Cowey, A. (2004) Chromatic edges, surfaces and constancies in cerebral achromatopsia. *Neuropsychologia* 42:821–30. [RWK]

Kentridge, R. W., Heywood, C. A. & Weiskrantz, L. (1999) Attention without awareness in blindsight. *Proceedings of the Royal Society of London: Biological Sciences* 266(1430):1805–11. [rNB]

Kentridge, R. W., Heywood, C. A. & Cowey, A. (2004) Chromatic edges, surfaces, and constancies in cerebral achromatopsia. *Neuropsychologia* 42(6):821–30. [rNB]

Kobes, B. (1995) Access and what it is like. *Behavioral and Brain Sciences* 18(2):260. [aNB]

Koch, C. (2004) *The quest for consciousness: A neurobiological approach.* Roberts. [aNB, CK, DM]

Koch, C. & Tsuchiya, N. (2007) Attention and consciousness: Two distinct brain processes. *Trends in Cognitive Sciences* 11:16–22. [rNB, CK, SK]

Kosslyn, S. M., Thompson, W. L. & Ganis, G. (2006) *The case for mental imagery*. Oxford University Press. [rNB]

Kouider, S., Dehaene, S., Jobert, A. & Le Bihan, D. (2007) Cerebral bases of subliminal and supraliminal priming during reading. *Cerebral Cortex* 17(9):2019–29. [arNB, SK, JP]

Kouider, S. & Dupoux, E. (2004) Partial awareness creates the "illusion" of subliminal semantic priming. *Psychological Science* 15(2):75–81. [rNB, SK]

(2007) How "semantic" is response priming restricted to practiced items? A reply to Abrams & Grinspan (2007). *Consciousness and Cognition* 16:954–56. [rNB]

Kourtzi, Z. & Kanwisher, N. (2000) Activation in human MT/MST by static images with implied motion. *Journal of Cognitive Neuroscience* 12:48–55. [aNB]

Kriegel, U. (2005) Naturalizing subjective character. *Philosophy and Phenomenological Research* 71:23–57. [aNB, WGL, DMR]

Kriegel, U. & Williford, K. (2006) *Self-representational approaches to consciousness.* MIT Press. [aNB]

Kriegeskorte, N., Sorger, B., Naumer, M., Scwarzbach, J., van den Boogert, E., Hussy, W. & Goebel, R. (2003) Human cortical object recognition from a visual motion flowfield. *Journal of Neuroscience* 23(4):1451. [aNB]

Kubler, A. & Neumann, N. (2005) Brain-computer interfaces – the key for the conscious brain locked into a paralyzed body. *Progress in Brain Research* 150:513–25. [AV]

Lamme, V. A. F. (2003) Why visual attention and awareness are different. *Trends in Cognitive Sciences* 7(1):12–18. [aNB, CK, RL, VAFL]

(2004) Separate neural definitions of visual consciousness and visual attention; a case for phenomenal awareness. *Neural Networks* 17:861–72. [VAFL]

(2006) Towards a true neural stance on consciousness. *Trends in Cognitive Sciences* 10(11):494–501. [aNB, RL]

Lamme, V. A. F. & Roelfsema, P. R. (2000) The distinct modes of vision offered by feedforward and recurrent processing. *Trends in Neuroscience* 23(11):571–79. [RL, VAFL, CS]

Lamme, V. A. F., Zipser, K. & Spekreijse, H. (1998) Figure-ground activity in primary visual cortex is suppressed by anesthesia. *Proceedings of the National Academy of Sciences USA* 95(6):3263–68. [RL, VAFL]

(2002) Masking interrupts figure-ground signals in V1. *Journal of Cognitive Neuroscience* 14(7):1044–53. [RL]

Landman, R., Spekreijse, H. & Lamme, V. A. F. (2003) Large capacity storage of integrated objects before change blindness. *Vision Research* 43(2):149–64. [AB, KB, arNB, TB, AC, RG, CK, RL, VAFL, LN, JKO, DMR, CS, MSh, MSp, RVG]

(2004) The role of figure-ground segregation in change blindness. *Psychonomic Bulletin and Review* 11(2):254–61. [RL]

Lau, H. C. & Passingham, R. E. (2006) Relative blindsight in normal observers and the neural correlate of visual consciousness. *Proceedings of the National Academy of Sciences USA* 103(49):18763–68. [HL, CS]

(2007) Unconscious activation of the cognitive control system in the human prefrontal cortex. *Journal of Neuroscience* 27:5805–11. [VAFL]

Laureys, S. (2005) The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences* 9(2):556–59. [aNB]

Laureys, S., Pellas, F., Van Eeckhout, P., Ghorbel, S., Schnakers, C., Perrin, F., Berré, J., Faymonville, M. E., Pantke, K. H., Damas, F., Lamy, M., Moonen, G. & Goldman, S. (2005) The locked-in syndrome: What is it like to be conscious but paralyzed and voiceless? *Progress in Brain Research* |V150: 495–511. [LN, AV]

Levine, J. (1983) Materialism and qualia: The explanatory gap. *Pacific Philosophical Quarterly* |V64:354–61. [aNB]

(2001) *Purple haze: The puzzle of consciousness.* Oxford University Press. [aNB]

(2006) Conscious awareness and (self)representation. In: *Self-representational approaches to consciousness*, ed. U. Kriegel & K, pp. 173–97. Williford. MIT Press. [aNB]

Levy, I., Hasson, U. & Malach, R. (2004) One picture is worth at least a million neurons. *Current Biology* 14(11):996–1001. [RM]

Lieberman, M. D., Eisenberger, N. I., Crockett, M. J., Tom, S. M., Pfeifer, J. H. & Way, B. M. (2007) Putting feelings into words: Affect labeling disrupts amygdala activity in response to affective stimuli. *Psychological Science* 18: 421–28. [CEI]

Llinás, R. R. (2001) *I of the vortex.* MIT Press. [aNB]

Llinás, R. R., Ribary, U., Contreras, D. & Pedroarena, C. (1998) The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society B* 353:1841–49. [aNB]

Locke, J. (1689/1975) An essay concerning human understanding. Clarenda Press. [rNB]

Loftus, G. & Irwin, D. (1998) On the relations among different measures of visible and informational persistence. *Cognitive Psychology* 35:135–99. [AB, arNB]

Logothetis, N. K. (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *Journal of Neuroscience* 23(10):3963–71. [CK]

Logothetis, N. K. & Wandell, B. A. (2004) Interpreting the BOLD signal. *Annual Review of Physiology* 66:735–69. [CK]

Long, G. (1980) Iconic memory: A review and critique of the study of short term visual storage. *Psychological Bulletin* 88:785–820. [aNB]

(1985) The variety of visual persistence: Comments on Yeomas and Irwin. *Perception and Psychophysics* 38:381–85. [aNB]

Luck, S. J. & Vogel, E. K. (1997) The capacity of visual working memory for features and conjunctions. *Nature* 390:279–81. [aNB]

Lumer, E. D., Friston, K. J. & Rees, G. (1998) Neural correlates of perceptual rivalry in the human brain. *Science* 280:1930–34. [CS]

Lumer, E. D. & Rees, G. (1999) Covariation of activity in visual and prefrontal cortex associated with subjective visual perception. *Proceedings of the National Academy of Sciences USA* 96(4):1669–73. [rNB, CS]

Lycan, W. (1996) *Consciousness and experience.* MIT Press. [arNB]

(2004) The superiority of HOP to HOT. In: *Higher-order theories of consciousness*, ed. R. Gennaro, pp. 93–114. John Benjamins. [rNB]

Mack, A. & Rock, I. (1998) *Inattentional blindness.* MIT Press. [CEI]

Mackay, D. J. C. (2004) *Information theory, inference, and learning algorithms.* Cambridge University Press. [OJH]

Macmillan, N. A. & Creelman, C. D. (1991) *Detection theory: A user's guide.* Cambridge University Press. [CS, MSn]

Marcel, A. J. (1993) Slippage in the unity of consciousness. In: *Experimental and theoretical studies of consciousness: The Ciba Foundation symposium*, ed. G. R. Bock & J. Marsh, p. 174. Wiley. [HL]

Mathiesen, C., Caesar, K., Akgoren, N. & Lauritzen, M. (1998) Modification of activity-dependent increases of cerebral blood flow by excitatory synaptic activity and spikes in rat cerebellar cortex. *Journal of Physiology* 512(Pt 2):555–66. [CK]

McCarty, M. E., Clifton, R. K. & Collard, R. R. (1999) Problem solving in infancy: The emergence of an action plan. *Developmental Psychology* 35:1091–101. [CEI]

McConkie, G. W. & Rayner, K. (1975) The span of the effective stimulus during a fixation in reading. *Perception and Psychophysics* 17:578–86. [arNB, SK]

McConkie, G. W. & Zola, D. (1979) Is visual information integrated across successive fixations in reading? *Perception and Psychophysics* 25:221–24. [arNB]

McDermott, D. (2001) *Mind and mechanism.* MIT Press. [DM]

McElree, B. (2006) Accessing recent events. In: *The psychology of learning and motivation, vol.* 46, ed. B. H. Ross, pp 155–201. Academic Press. [aNB]

McGinn, C. (1991) *The problem of consciousness.* Oxford University Press. [aNB]

McLaughlin, B. P. (1992) The rise and fall of British emergentism. In: *Emergence or reduction?: Prospects for nonreductive physicalism*, ed. A. Beckermann, H. Flohr & J. Kim, pp. 49–93. De Gruyter. [aNB]

McRae, K., Butler, B. E. & Popiel, S. J. (1987) Spatiotopic and retinotopic components of iconic memory. *Psychological Research* 49(4):221–27. [RL]

Meadows, J. C. (1974) Disturbed perception of colours associated with localized cerebral lesions. *Brain* 97:615–32. [RWK]

Merikle, P., Joordens, S. & Stolz, J. (1995) Measuring the relative magnitude of unconscious influences. *Consciousness and Cognition* 4:422–39. [MSn]

Merker, B. (2007) Consciousness without a cerebral cortex: A challenge for neuroscience and medicine. *Behavioral and Brain Sciences* 30:63–81. [aNB, CEI]

Metzinger, T. (2003) *Being no one.* MIT Press. [aNB]

Miller, G. (1956) The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychological Review* 63:81–97. [aNB]

Milner, A. D. & Goodale, M. A. (1995) *The visual brain in action.* Oxford University Press. [CEI]

(2008) Two visual systems re-viewed. *Neuropsychologia* 46:774–85. [rNB]

Minsky, M. (1986) *The society of mind.* Simon & Schuster. [aNB]

Montague, D. P. F. & Walker-Andrews, A. S. (2001) Peekaboo: A new look at infants' perception of emotion expressions. *Developmental Psychology* 37:826–38. [CEI]

Most, S. B., Chun, M. M., Widders, D. M. & Zald, D. H. (2005a) Attentional rubbernecking: Cognitive control and personality in emotion-induced blindness. *Psychonomic Bulletin and Review* 12:654–61. [CEI]

Most, S. B., Scholl, B. J., Clifford, E. R. & Simons, D. J. (2005b) What you see is what you set: Sustained inattentional blindness and the capture of awareness. *Psychological Review* 112:217–42. [CEI]

Most, S. B., Simons, D. J., Scholl, B. J., Jimenez, R., Clifford, E. & Chabris, C. F. (2001) How not to be seen: The contribution of similarity and selective ignoring to sustained inattentional blindness. *Psychological Science* 12:9–17. [CEI]

Muir, D. & Lee, K. (2003) The still-face effect: Methodological issues and new applications. *Infancy* 4:483–91. [CEI]

Mullen, K. T. (1992) Colour vision as a post-receptoral specialization of the central visual field. *Vision Research* 31(1):119–30. [rNB]

Naccache, L. (2006a) *Le nouvel inconscient. Freud, Christophe Colomb des neurosciences.* Odile Jacob. [LN]

(2006b) Psychology. Is she conscious? *Science* 313(5792):1395–96. [aNB, LN, CS]

Nachev, P. & Husain, M. (2007) Comment on "Detecting awareness in the vegetative state." *Science* 315(5816):1221; author reply: 1221. [CS]

Nagel, T. (1974) What is it like to be a bat? *The Philosophical Review* 83(4):435–50. [aNB]

Nakayama, K. (1990) The iconic bottleneck and the tenuous link between early visual processing and perception. In: *Vision: Coding and efficiency*, ed. C. Blakemore, pp. 411–22. Cambridge University Press. [aNB]

Nakayama, K., He, Z. J. & Shimojo, S. (1995) Visual surface representation: A critical link between lower-level and higher-level vision. In: *Visual cognition: An invitation to cognitive science*, vol. 2, ed. S. M. Kosslyn & D. Osherson, pp. 1–70. MIT Press. [aNB]

Nature, Editorial (2006) Flickers of consciousness. *Nature* 443(7108):121–22. [aNB]

Noë, A. (2002) Is the visual world a grand illusion? *Journal of Consciousness Studies* 9(5–6):1–12. [aNB]

(2004) *Action in perception.* MIT Press. [aNB]

(2005) What does change blindness teach us about consciousness? *Trends in Cognitive Sciences* 9(5):218. [aNB]

Noë, A. & Thompson, E. (2004) Are there neural correlates of consciousness? *Journal Of Consciousness Studies* 11(1):3–28. [aNB]

O'Craven, K. & Kanwisher, N. (2000) Mental imagery of faces and places activates corresponding stimulus-specific brain regions. *Journal of Cognitive Neuroscience* 12:1013–23. [aNB]

O'Regan, J. K. & Noë, A. (2001) A sensorimotor approach to vision and visual consciousness. *Behavioral and Brain Sciences* 24:883–975. [aNB]

O'Regan, K. (1992) Solving the "real" mysteries of visual perception: The world as an outside memory. *Canadian Journal of Psychology* 46(3):461–88. [aNB]

Oakes, L. M. & Ribar, R. J. (2005) A comparison of infants' categorization in paired and successive presentation familiarization tasks. *Infancy* 7:85–98. [CEI]

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S. & Pickard, J. D. (2006) Detecting awareness in the vegetative state. *Science* 313(5792):1402. [aNB, LN, CS, AV]

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., Jolles, D. & Pickard, J. (2007) Response to comments on "Detecting awareness in the vegetative state." *Science* 315(5816):1221c. [AV]

Papineau, D. (1998) Functionalism. In: *Routledge encyclopedia of philosophy*, ed. E. Craig. Routledge. (Web-based encyclopedia.) Retrieved April 22, 2007 from: http://www.rep.routledge.com/article/V015SECT4 [aNB]

(2002) *Thinking about consciousness.* Oxford University Press. [aNB, KB, DP]

Pascual-Leone, A. & Walsh, V. (2001) Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 292(5516):510–12. [aNB, OJH, HL, RL]

Pearson, D. G. (2001) Imagery and the visuo-spatial sketchpad. In: *Working memory in perspective*, ed. J. Andrade. *Psychology Press.* [TB]

Peirce, C. S. (1903) *Collected papers of Charles Sanders Peirce.* Harvard University Press. [aNB]

Persaud, N. & McLeod, P. (2007) Wagering demonstrates subconscious processing in a binary exclusion task. *Consciousness and Cognition.* DOI:10.1016/.concog.2007.05.003. [HL]

Persaud, N., McLeod, P. & Cowey, A. (2007) Post-decision wagering objectively measures awareness. *Nature Neuroscience* 10:257–61. [HL, CS]

Phillips, W. A. (1974) On the distinction between sensory storage and short-term visual memory. *Perception and Psychophysics* 16:283–90. [aNB]

Piattelli-Palmarini, M. (1994) *Inevitable illusions: How mistakes of reason rule our minds.* Wiley. [aNB]

Pins, D. & Ffytche, D. H. (2003) The neural correlates of conscious vision. *Cerebral Cortex* 13:461–74. [aNB]

Pollen, D. A. (1999) On the neural correlates of visual perception. *Cerebral Cortex* 9(1):4–19. [aNB, OJH]

(2003) Explicit neural representations, recursive neural networks and conscious visual perception. *Cerebral Cortex* 13:807–14. [aNB]

(in press) The fundamental requirements for primary visual perception. *Cerebral Cortex*. Advance access published on December 17, 2007; doi:10.1093/Cercor/bhm226. [aNB]

Potter, M. C. (1993) Very short-term conceptual memory. *Memory and Cognition* 21(2):151–61. [aNB]

Prinz, J. J. (2000) A neurofunctional theory of visual consciousness. *Consciousness and Cognition* 9(2):243–59. [arNB]

(2005) A neurofunctional theory of consciousness. In: *Cognition and the brain: Philosophy and the neuroscience movement*, ed. A. Brook & K. Akins, pp. 381–96. Cambridge University Press. [rNB, JP]

(2007) Mental pointing: Phenomenal knowledge without concepts. *Journal of Consciousness Studies* 14(9–10):184–211. [JP]

(forthcoming) *The conscious brain*. Oxford University Press. [JP]

Putnam, H. (1975) The meaning of "meaning." *Minnesota Studies in the Philosophy of Science* 7:131–93. [aNB]

(1981) *Reason, truth and history.* Cambridge University Press. [aNB]

Pylylshyn, Z. (2003) *Seeing and visualizing.* MIT Press. [aNB]

Qiu, J. (2006) Does it hurt? *Nature* 444(9):143–45. [rNB]

Quine, W. V. (1969) Natural kinds. In: *Ontological reality and other essays*, ed. W. V. Quine, pp.114–39. Columbia University Press. [aNB]

Quinn, P. C. (2006) On the emergence of perceptual organization and categorization in young infants: Roles for perceptual process and knowledge access. In: *Child psychology: A handbook of contemporary issues*, 2nd edition, ed. L. Balter & C. Tamis-LeMonda, pp. 109–31. Psychology Press/Taylor & Francis. [CEI]

Quinn, P. C. & Eimas, P. D. (1996) Perceptual organization and categorization in young infants. In: *Advances in infancy research*, vol. *10*, ed. C. Rovee-Collier & L. P. Lipsitt, pp. 1–36. Ablex. [CEI]

(1997) A reexamination of the perceptual-to-conceptual shift in mental representations. *Review of General Psychology* 1:271–87. [CEI]

Quinn, P. C., Eimas, P. D. & Rosenkrantz, S. L. (1993) Evidence for representations of perceptually similar natural categories by 3- and 4-month-old infants. *Perception* 22:463–75. [CEI]

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A. & Shulman, G. L. (2001) A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 98(2):676–82. [rNB, RM]

Raymond, J. E., Shapiro, K. L. & Arnell, K. M. (1992) Temporary suppression of visual processing during RSVP: An attentional blink? *Journal of Experimental Psychology: Human Perception and Performance* 18:849–60. [CEI]

Rayner, K. & Bertera, J. H. (1979) Reading without a fovea. *Science* 206(4417):468–69. [LN]

Reddy, L., Wilken, P. & Koch, C. (2004) Face-gender discrimination is possible in the near absence of attention. *Journal of Vision* 4:106–17. [CK]

Rees, G., Kreiman, G. & Koch, C. (2002a) Neural correlates of consciousness in humans. *Nature Reviews Neuroscience* 3(4):261–70. [aNB, CS]

Rees, G., Wojciulik, E., Clarke, K., Husain, M., Frith, C. & Driver, J. (2000) Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction. *Brain* 123(Pt 8):1624–33. [aNB, CK, CS]

(2002b) Neural correlates of conscious and unconscious vision in parietal extinction. *Neurocase* 8:387–93. [aNB, CK]

Reiss, J. E. & Hoffman, J. E. (2006) Object substitution masking interferes with semantic processing: Evidence from event-related potentials. *Psychological Science* 17:1015–20. [CEI]

Rensink, R. A., O'Regan, J. K. & Clark, J. J. (1997) To see or not to see: The need for attention to perceive changes in scenes. *Psychological Science* 8:368–73. [aNB]

Rosenberg, A. (2005) *Philosophy of science: A contemporary introduction*. Routledge. [rNB]

Rosenthal, D. (2005) *Consciousness and mind.* Oxford University Press. [aNB, DMR]

Ross, W. D., (1955) Aristotle: On dreams. In: *Aristotle. Parva naturalia*, ed. W. D. Ross, pp. 175–223. Clarendon Press. [aNB]

Ross, W. D., ed. (1961) *Aristotle's De anima.* Clarendon Press. [aNB]

Rousselet, G., Fabre-Thorpe, M. & Thorpe, S. (2002) Parallel processing in high-level visual scene categorization. *Nature Neuroscience* 5:629–30. [aNB]

Rousselet, G. A., Thorpe, S. J. & Fabre-Thorpe, M. (2004a) How parallel is visual processing in the ventral pathway? *Trends in Cognitive Science* 8:363–70. [TB]

(2004b) Processing of one, two, or four natural scenes in humans: The limits of parallelism. *Vision Research* 44: 877–94. [TB]

Ruff, C. C., Kristjansson, A. & Driver, J. (in press) Readout from iconic memory involves similar neural processes as selective spatial attention. *Psychological Science*. [CS]

Sackeim, H. A., Nordlie, J. W. & Gur, R. C. (1979) A model of hysterical and hypnotic blindness: Cognition, motivation, and awareness. *Journal of Abnormal Psychology* 88(5):474–89. [CK]

Scholte, H. S., Witteveen, S. C., Spekreijse, H. & Lamme, V. A. F. (2006) The influence of inattention on the neural correlates of scene segmentation. *Brain Research* 1076:106–15. [VAFL]

Searle, J. (1992) *The rediscovery of the mind.* MIT Press. [aNB]

(2005) Consciousness: What we still don't know. *The New York Review of Books* 52(1)36–39. [aNB]

Sergent, C., Baillet, S. & Dehaene, S. (2005) Timing of the brain events underlying access to consciousness during the attentional blink. *Nature Neuroscience* 8(10):1391–400. [VAFL, CS, LN]

Sergent, C. & Dehaene, S. (2004) Is consciousness a gradual phenomenon? Evidence for an all-or-none bifurcation during the attentional blink. *Psychological Science* 15:720–28. [arNB, CS]

Shanahan, M. P. (2005) Global access, embodiment, and the conscious subject. *Journal of Consciousness Studies* 12(12):46–66. [MSh]

(in press) A spiking neuron model of cortical broadcast and competition. *Consciousness and Cognition*. [MSh]

Shanahan, M. P. & Baars, B. J. (2005) Applying global workspace theory to the frame problem. *Cognition* 98(2):157–76. [MSh]

Shoemaker, S. (1981) Some varieties of functionalism. *Philosophical Topics* 12:93–119. [aNB]

Siegel, S. (2006a) The contents of perception. In: *The Stanford encyclopedia of philosophy*, ed. E. N. Zalta, pp. Online publication. Available at: http://plato.stanford.edu/archives/spr2006/entries/perception-contents/ [aNB]

(2006b) Which properties are represented in perception? In: *Perceptual experience*, ed. T. Gendler & J. Hawthorne, pp. 481–503. Oxford University Press. [aNB]

Silvanto, J., Cowey, A., Lavie, N. & Walsh, V. (2005a) Striate cortex (V1) activity gates awareness of motion. *Nature Neuroscience* 8(2):143–44. [aNB]

Silvanto, J., Lavie, N. & Walsh, V. (2005b) Double dissociation of V1 and V5/MT activity in visual awareness. *Cerebral Cortex* 15:1736–41. [aNB, VAFL]

Simons, D. J. (1997) Change blindness. *Trends in Cognitive Sciences* 1:261–67. [aNB]

Simons, D. J. & Ambinder, M. (2005) Change blindness: Theory and consequences. *Current Directions in Psychological Science* 14:44–48. [aNB]

Simons, D. J. & Chabris, C. F. (1999) Gorillas in our midst: Sustained inattentional blindness for dynamic events. *Perception* 28:1059–74. [CEI]

Simons, D. J. & Rensink, R. (2005a) Change blindness: Past, present and future. *Trends in Cognitive Sciences* 9(1):16–20. [aNB]

(2005b) Change blindness, representations and consciousness: Reply to Noë. *Trends in Cognitive Sciences* 9(5):219. [aNB]

Singer, W. (1995) Development and plasticity of cortical processing architectures. *Science* 270:758–64. [VAFL]

Slater, A. & Lewis, M., eds. (2007) *Introduction to infant development*, 2nd edition. Oxford University Press. [CEI]

Slater, R., Cantarella, A., Gallella, S., Worley, A., Boyd, S., Meek, J. & Firzgerald, M. (2006) Cortical pain responses in human infants. *The Journal of Neuroscience* 26(14):3662–66. [aNB]

Sligte, I. G., Scholte, H. S. & Lamme, V. A. F. (2008) Are there multiple visual short-term memory stores? *Plos One* 3(2):1–9. [AB, arNB, TB, RL, JKO, MSp]

Smith, D. W. (1986) The structure of (self-)consciousness. *Topoi* 5:149–56. [aNB]

Snodgrass, M. (2002) Disambiguating conscious and unconscious inferences: Do exclusion paradigms demonstrate unconscious perception? *American Journal of Psychology* 115:545–80. [rNB, MSn]

Snodgrass, M., Bernat, E. & Shevrin, H. (2004) Unconscious perception: A model-based approach to method and evidence. *Perception and Psychophysics* 66:846–67. [MSn]

Snodgrass, M. & Shevrin, H. (2006) Unconscious inhibition and facilitation at the objective detection threshold. *Cognition* 101(1):43–79. [aNB, MSn]

Solomon, J. (2004) The effects of spatial cues on visual sensitivity. *Vision Research* 44:1209–16. [RWK]

Sommerville, J. A. & Woodward, A. L. (2005) Pulling out the intentional structure of action: The relation between action processing and action production in infancy. *Cognition* 95:1–30. [CEI]

Sommerville, J. A., Woodward, A. L. & Needham, A. (2005) Action experience alters 3-month-old infants' perception of others' actions. *Cognition* 96:B1–B11. [rNB]

Sosa, E. (2002) Privileged access. In: *Consciousness: New philosophical perspectives*, ed. Q. Smith & A. Jokic, pp. 273–94. Oxford University Press. [aNB]

Spener, M. (under review) Phenomenal adequacy and introspective evidence. [MSp]

Sperber, D. (2001) In defense of massive modularity. In: *Language, brain and cognitive development: Essays in honor of Jacques Mehler*, ed. E. Dupoux, pp. 47–57. MIT Press. [aNB]

Sperling, G. (1960) The information available in brief visual presentations. *Psychological Monographs: General and Applied* 74(11, Whole No. 498):1–29. [Whole issue.] [KB, arNB, TB, AC, RG, GH, CK, SK, DM, LN, JKO, DP, DMR, CS, MSh, MSp, MT, RVG]

Srinivasan, R., Russell, D. P., Edelman, G. M. & Tononi, G. (1999) Increased synchronization of neuromagnetic responses during conscious perception. *Journal of Neuroscience* 19(13):5435–48. [CS]

Stern, D. N. (1974) *Mother and infant at play: The dyadic interaction involving facial, vocal, and gaze behavior*. Wiley. [CEI]

Stoerig, P. (2001) The neuroanatomy of phenomenal vision: A psychological perspective. In: *Cajal and consciousness: Scientific approaches to consciousness on the centennial of Ramon y Cajal's Textura*, ed. P. C. Marijuan, pp. 176–94. Annals of the New York Academy of Sciences. [aNB]

Strawson, G. (2003) What is the relation between an experience, the subject of the experience, and the content of the experience? *Philosophical Issues* 13(1):279–315. [aNB]

Supèr, H., Spekreijse, H. & Lamme, V. A. F. (2001a) A neural correlate of working memory in the monkey primary visual cortex. *Science* 293:120–24. [arNB]

(2001b) Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). *Nature Neuroscience* 4(3):304–10. [aNB, VAFL, RL]

Taddio, A., Goldbach, M., Ipp, M., Stevens, B. & Koren, G. (1995) Effect of neonatal circumcision on pain responses during vaccination in boys. *The Lancet* 345(8945):291–92. [rNB]

Tavalaro, J. & Tayson, R. (1997) *Look up for yes*. Kodansha America. [AV]

The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (1). *New England Journal of Medicine* 330(21):1499–508. [AV]

Theoret, H., Kobayashi, M., Ganis, G., Di Capua, P. & Pascual-Leone, A. (2002) Repetitive transcranial magnetic stimulation of human area MT/V5 disrupts perception and storage of the motion aftereffect. *Neuropsychologia* 40(13):2280–87. [aNB]

Thomas, N. (1999) Are theories of imagery theories of imagination? *Cognitive Science* 23(2):207–45. [aNB]

Thompson, K. G. & Schall, J. D. (1999) The detection of visual signals by macaque frontal eye field during masking. *Nature Neuroscience* 2:283–88. [VAFL]

Tong, F., Nakayama, K., Vaughan, J. T. & Kanwisher, N. (1998) Binocular rivalry and visual awareness in human extrastriate cortex. *Neuron* 21(4):753–59. [aNB]

Tononi, G. & Edelman, G. M. (1998) Consciousness and complexity. *Science* 282:1846–51. [aNB]

Treisman, A., Russell, R. & Green, J. (1975) Brief visual storage of shape and movement. In: *Attention and performance*, ed. S. Dornic & P. Rabbitt, pp. 699–721. Academic Press. [arNB]

Treue, S. & Martìnez Trujillo, J. C. (1999) Feature-based attention influences motion processing gain in macaque visual cortex. *Nature* 399:575–79. [RWK]

Tronick, E. Z. (1989) Emotions and emotional communication in infants. *American Psychologist* 44:112–19. [CEI]

Tsao, D. Y., Tootell, R. B. H. & Livingstone, M. S. (2006) A cortical region consisting entirely of face-selective cells. *Science* 311(5761):670–74. [aNB]

Tse, P. U., Martinez-Conde, S., Schlegel, A. A. & Macknik, S. L. (2005) Visibility, visual awareness and visual masking of simple unattended targets are confined to areas in the occipital cortex beyond human V1/V2. *Proceedings of the National Academy of Sciences USA* 102:17178–83. [arNB]

Tsuchiya, N. & Koch, C. (2008) The relationship between consciousness and attention. In: *The neurology of consciousness*, ed. S. Laureys & G. Tononi. Elsevier. [CK]

Uebel, T. (2006) Vienna Circle. *The Stanford Encyclopedia of Philosophy Fall 2006 Edition*, ed. E. N. Zalta. Online publication. Available at: http://plato.stanford.edu/archives/fall2006/entries/vienna-circle [aNB]

VanRullen, R. V. & Thorpe, S. J. (2001) Is it a bird? Is it a plane? Ultra-rapid visual categorization of natural and artificial objects. *Perception* 30:655–68. [TB]

Verfaellie, M., Milberg, W. P., McGlinchey-Berroth, R., Grande, L. & D'Esposito, M. (1995) Comparison of cross-field matching and forced-choice identification in hemispatial neglect. *Neuropsychology* 9:427–34. [rNB]

Visser, T. & Merikle, P. (1999) Conscious and unconscious processes: The effects of motivation. *Consciousness and Cognition* 8:94–113. [MSn]

Vogel, E. K., Woodman, G. F. & Luck, S. J. (2001) Storage of features, conjunctions and objects in visual working memory. *Journal of Experimental Psychology: Human Perception and Performance* 27:92–114. [aNB]

Volpe, B. T., LeDoux, J. E. & Gazzaniga, M. S. (1979) Information processing of visual stimuli in an extinguished field. *Nature* 282:722–24. [rNB]

Vorberg, D., Mattler, U., Heinecke, A., Schmidt, T. & Schwarzbach, J. (2003) Different time courses for visual perception and action priming. *Proceedings of the National Academy of Sciences USA* 100(10):6275–80. [CS]

Walker-Andrews, A. S. (1998) Emotions and social development: Infants' recognition of emotions in others. *Pediatrics* 102:1268–71. [CEI]

Weiskrantz, L. (1986) *Blindsight: A case study and implications.* Oxford University Press. [HL]

(1997) *Consciousness lost and found: A neuropsychological exploration*. Oxford University Press. [aNB, CS]

Weiskrantz, L., Cowey, A. & Hodinott-Hill, I. (2002) Prime-sight in a blindsight subject. *Nature Neuroscience* 5:101–102. [aNB]

Wilhelm, B., Jordan, M. & Birbaumer, N. (2006) Communication in locked-in syndrome: Effects of imagery on salivary pH. *Neurology* 67(3):534–35. [AV]

Wilken, P. (2001) *Capacity limits for the detection and identification of change: Implications for models of visual short-term memory.* University of Melbourne Press. [aNB]

Williams, M. A., Dang, S. & Kanwisher, N. G. (2007) Only some spatial patterns of fMRI response are read out in task performance. *Nature Neuroscience* 10(6):685–86. [LN]

Wolfe, J. (1999) Inattentional amnesia. In: *Fleeting memories*, ed. V. Coltheart, pp. 71–94. MIT Press. [aNB]

Woodman, G. F. & Luck, S. J. (2003) Dissociations among attention, perception, and awareness during obect-substitution masking. *Psychological Science* 14:605–11. [CEI]

Xu, Y. (2002) Encoding colour and shape from different parts of an object in visual short-term memory. *Perception and Psychophysics* 64:1260–80. [aNB]

Xu, Y. & Chun, M. M. (2006) Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature* 440:91–95. [aNB]

Yang, W. (1999) *Lifetime of human visual sensory memory: Properties and neural substrate.* New York University Press. [aNB]

Zeki, S. (2001) Localization and globalization in conscious vision. *Annual Review of Neuroscience* 24:57–86. [aNB]

Zeki, S. & Bartels, A. (1999) Toward a theory of visual consciousness. *Consciousness and Cognition* 8(2):225–59. [aNB, OJH]

Zeki, S. & ffytche, D. H. (1998) The Ridoch syndrome: Insights into the neurobiology of conscious vision. *Brain* 121(Pt 1):25–45. [aNB, OJH]

Zihl, J., von Cramon, D. & Mai, N. (1983) Selective disturbance of movement vision after bilateral brain damage. *Brain* 106:313–40. [aNB]

Neuroradiology
DOI 10.1007/s00234-009-0614-8

INVITED REVIEW

Neuroimaging after coma

Luaba Tshibanda · Audrey Vanhaudenhuyse · Mélanie Boly · Andrea Soddu · Marie-Aurelie Bruno · Gustave Moonen · Steven Laureys · Quentin Noirhomme

Received: 7 September 2009 / Accepted: 7 October 2009
© Springer-Verlag 2009

Abstract Following coma, some patients will recover wakefulness without signs of consciousness (only showing reflex movements, i.e., the vegetative state) or may show non-reflex movements but remain without functional communication (i.e., the minimally conscious state). Currently, there remains a high rate of misdiagnosis of the vegetative state (Schnakers et. al. BMC Neurol, 9:35, 8) and the clinical and electrophysiological markers of outcome from the vegetative and minimally conscious states remain unsatisfactory. This should incite clinicians to use multimodal assessment to detect objective signs of consciousness and validate para-clinical prognostic markers in these challenging patients. This review will focus on advanced magnetic resonance imaging (MRI) techniques such as magnetic resonance spectroscopy, diffusion tensor imaging, and functional MRI (fMRI studies in both "activation" and "resting state" conditions) that were recently introduced in the assessment of patients with chronic disorders of consciousness.

Keywords Vegetative state · Diffusion tensor imaging · MR spectroscopy · Functional MRI · Consciousness

Introduction

Progress in emergency medicine and reanimation has increased the number of patients who survive severe acute brain damage [1]. The majority of these patients recover and transit through different clinical stages. Coma is characterized by the complete failure of the arousal system with no spontaneous eye opening, and results from a structural or metabolic lesion of the brainstem reticular system or from widespread bilateral cerebral damage. These patients will never open their eyes even when intensively stimulated [2]. Coma is usually a transient condition which will last no longer than a few days or weeks. Some patients may evolve to brain death (i.e., irreversible coma with absent brainstem function); others will progress to a vegetative state. Vegetative state is characterized by the complete absence of behavioral evidence for self or environmental awareness with the capacity for spontaneous or stimulus-induced arousal, evidenced by sleep–wake cycles [3]. It is mainly caused by diffuse axonal injury which interrupts the white matter connections between the cortex and thalamus or by diffuse cortical damage in case of cardiorespiratory arrest. Many patients in vegetative state regain consciousness in the first month after brain injury. However, if patients show no sign of awareness 1 year after a traumatic brain injury or three months after brain damage from lack of oxygen, the chances of recovery are considered close to zero, and the patient is considered in a permanent vegetative state [3]. Those who recover from vegetative state, typically progress through different stages before fully or partially (minimally conscious state)

Thibanda and Vanhaudenhuyse contributed equally to this paper.

L. Tshibanda · A. Vanhaudenhuyse · M. Boly · A. Soddu · M.-A. Bruno · S. Laureys (✉) · Q. Noirhomme
Coma Science Group, Cyclotron Research Center,
University and University Hospital of Liège,
Sart-Tilman,
B30 Liège, Belgium
e-mail: steven.laureys@ulg.ac.be

L. Tshibanda · M. Boly · S. Laureys
Department of Neuroradiology, University Hospital of Liège,
Sart-Tilman,
Liège, Belgium

M. Boly · G. Moonen · S. Laureys
Department of Neurology, University Hospital of Liège,
Sart-Tilman,
Liège, Belgium

Published online: 28 October 2009

recovering consciousness. Minimally conscious patients are unable to communicate their thoughts and feelings, but demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment [4]. Minimally conscious patients have to show at least one of the following behaviors: oriented response to noxious stimuli, sustained visual pursuit, command following, intelligible verbalization or emotional or motor behaviors that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Like the vegetative state, the minimally conscious state may be chronic and sometimes permanent. However, at present, no time intervals for "permanent minimally conscious state" have been agreed upon. These patients have a distribution of brain damage similar to that of vegetative patients with less severe lesion. Patients who emerge from the minimally conscious state are characterized by the ability to use functional interactive communication or functional use of objects [4]. Finally, patients may awaken from their coma fully aware but unable to move or speak—their only way to communicate is via small eye movements (locked-in syndrome). The locked-in syndrome, characterized by quadriplegia and anarthria with general preservation of cognition and vertical eye movement, describes patients who are awake and conscious but have no means of producing speech, limb, or facial movements. It is caused by hemorrhage or an infarction of the pontine tegmentum and must be distinguished from disorders of consciousness [5].

An accurate and reliable evaluation of the level and content of consciousness in severely brain-damaged patients is of paramount importance for their appropriate management. The clinical evaluation of consciousness in non-communicative patients remains erroneous in 40% of cases [6–8]. Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination (i.e., assessing command following). Neuroimaging techniques such as proton MR spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI) have improved the quantification of neuronal damage and offers the possibility of directly measuring the brain's activity, not only at rest or during passive stimulation, but also in response to commands [1, 9]. This review focuses on the clinical application of DTI, MRS, and fMRI in vegetative and minimally conscious state patients. These techniques have played a key role in the transition of clinical MRI from a discipline based on morphology to one that combines structure with function.

Imaging of consciousness disorders

A comprehensive exploration of patients with disorders of consciousness should assess all structures involved in arousal and awareness functions, namely, the ascending reticular activating system located in the postero-superior part of the brainstem (primary arousal structure) [2, 10] and a large set of supratentorial structures responsible of awareness, encompassing thalamus, basal forebrain, and fronto-parietal association cortices [11]. Brain imaging of patients with consciousness disorders is routinely performed on 1.5 or 3-T MR scanners. There are potential limitations to this exploration, including patient motion, uncontrolled intracranial pressure, risks associated with the transportation of the sedated and ventilated patient from intensive care unit to the MRI suite and brain edema. The timing of the MR examination also remains a subject of debate. Taking into account the time since traumatic brain injury (TBI) or stroke, there are four clinical phases to be distinguished: (1) an acute phase, which lasts 24 h after TBI; (2) an early subacute phase, from day 1 to 13; (3) a late subacute phase, from days 14 to 20, and (4) a chronic phase, which starts on day 21 [12]. When performed in the acute phase, the exploration may take into account reversible lesions such as edema but can miss secondary lesions due to intracranial hypertension or systemic disorders [13–15]. On the contrary, an examination performed late after the injury may only detect sequels such as non-specific global atrophy [16] and will have less impact on medical management or prognosis [17–20]. An early subacute examination with precise evaluation of the brain damage is critical for therapeutic decisions (i.e., to determine outcome, cognitive and behavioral deficits [21, 22]). The late subacute phase seems to be the best moment to assess disorders of consciousness, taking into account the physiopathology (subsiding brain edema) and the medical and ethical issues raised by the management of these patients [23, 24].

Conventional MR imaging The morphologic MRI acquisitions usually include non-contrast-enhanced sagittal T1, axial diffusion, axial fluid attenuated inversion recovery (FLAIR), axial T2-SE, coronal T2* sequences and a 3D T1-weighted volume acquisition. FLAIR and T2-SE sequences permit to detect brain edema, contusion, hematoma, herniation, subarachnoid hemorrhage, or hydrocephalus. T2* sequences are useful in detecting hemorrhagic diffuse axonal injuries (DAI) [25, 26]. The total number of lesions detected by FLAIR and T2* are shown to be inversely correlated with Glasgow Outcome Scale (GOS [27]) of traumatic coma patients [21, 28]; while the 3D T1 sequence provides an opportunity to evaluate the brain atrophy during the follow up of these patients [16]. A lot of studies performed on traumatic coma patients with conventional

MRI showed that lesions of the pons, midbrain, and basal ganglia were predictive of poor outcome especially when they are bilateral [29–39]. Despite their encouraging results, these studies fail to explain why some patients in vegetative state or with long-term marked cognitive impairments have no or minimal lesions on conventional MRI examination. This raises the question of the lack of specificity and insufficient sensitivity of conventional MR sequences which fail to reveal lesions such as ischemic axonal injuries. Therefore, it is clear that morphological MRI alone cannot be considered as a reliable tool to assess consciousness disorders severity or to predict their evolution.

Diffusion tensor imaging DTI is an extension of diffusion-weighted imaging which is based on the principle that water molecule movement is restricted by barriers to diffusion in the brain depending on tissue organization (Fig. 1). The diffusion of water protons is higher along fiber tracts than across them in the white matter, which allows for directional measurement of diffusion and, hence, measurement of structural integrity. DTI data can be used to compute the fractional anisotropy as well as to track fibers. The fractional anisotropy quantifies anisotropic diffusion in the brain, which is related to the density, integrity, and directionality of white matter tracts [40, 41]. DTI evaluates the architectural organization of white matter fibers and is a powerful technique for in vivo detection of diffuse axonal injury after brain trauma [42]. Advantages of DTI are numerous: (1) it can permit to evaluate brain trauma in sedated patient; (2) DTI measures are not influenced by sedatives or hypnotics unlike the clinical scores; (3) changes in fractional anisotropy may help to evaluate response to treatment even if the clinical scores are insufficient to assess the patient; (4) it may be an important surrogate marker.

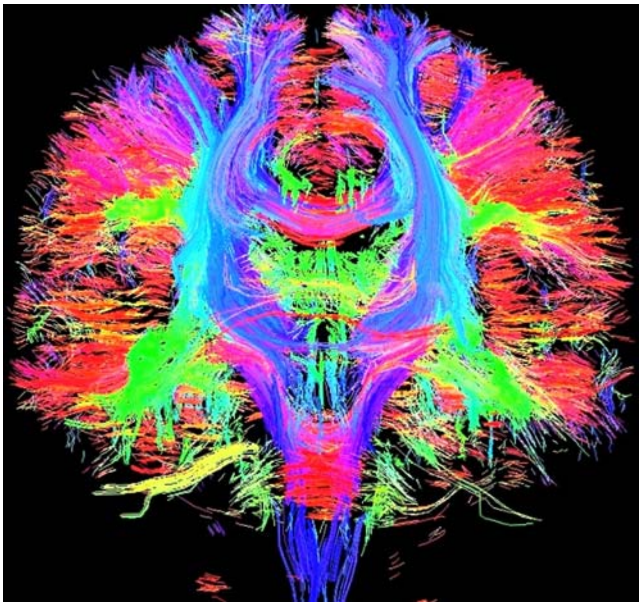


Fig. 1 Illustration of white matter tracts as visualized by diffusion tensor imaging in a healthy volunteers subject (*Blue*=*z*, *red*=*x*, *green*=*y* axes; TR/TE: 5700/90 ms, slices: 40, voxel size: 1.8×1.8×2.0 mm^3, FoV: 230×230 mm^2, bandwidth: 1,860 Hz/Px, diffusion weights: *b*=0, *b*=500, *b*=1,000)

The acquisition protocol, image processing, analysis, and interpretation of DTI are now routinely performed in clinical conditions essentially in the exploration of brain tumor. Studies on diffuse axonal injury [43, 44], as well as in other pathologies such as in patients with HIV [45] have shown that DTI may reveal damage in tissue appearing normal on conventional MRI sequences. In TBI patients, a significant negative correlation was reported between fractional anisotropy in the splenium of the corpus callosum and in the internal capsule and Glasgow Coma Scale (GCS [46]) score at discharge [13]. In a first study evaluating the combination of DTI and MRS as a tool for predicting long-term outcome of traumatic patients, Tollard et al. [24] observed that fractional anisotropy was significantly lower in patients who did not recover at all measurement sites, except in the posterior pons. They showed that prediction of non-recovery after 1 year could be calculated with up to 86% sensitivity and 97% specificity when taking into account both DTI and MRS values. Non-recovery of traumatic patients was also shown to be correlated with decreased fractional anisotropy in cerebral peduncle, posterior limb of the internal capsule, posterior corpus callosum, and inferior longitudinal fasciculus [47]. These studies confirm the relevance of the use of DTI as biomarker for consciousness recovery after a traumatic brain injury and support the possible use of this biomarker for early classification of patients. Furthermore, DTI recently revealed axonal regrowth in a patient who had been in a minimally conscious state but recovered verbal communication nearly two decades after a traumatic brain injury [48]. This demonstration of axonal regrowth after such a long time interval disproved the old dogma that neural plasticity is limited to the acute or subacute phase of cerebral injury.

Proton MR spectroscopy MRS is a noninvasive imaging method that provides useful metabolic information on brain damage that may not be visible on morphologic imaging. It has a better sensitivity than T2*sequences in the detection of ischemic or hemorrhagic diffuse axonal lesions in TBI [49]. Classically, the exploration of disorders of consciousness is performed at intermediate or long echo time (135–288 ms) and the main metabolites detected are choline (Cho), creatine (Cr), *N*-acetylaspartate (NAA), and lactate (La). Choline is a metabolic marker of membrane synthesis and catabolism. Its rate is slightly higher in white than in gray matter and increases when there is an important membrane turnover due to cell proliferation or inflammatory process. Creatine is considered as a marker of the aerobic energy metabolism. It is used for calculating metabolite ratios such as NAA/Cr and Cho/Cr ratios. *N*-acetylaspartate is found in both gray and white matter in approximately equal quantities as a marker of neuronal density and viability produced in the mitochondria of the neurons and transported into the neuronal cytoplasm and the axons. In healthy subjects, there is an increase in NAA in gray matter from ventral to dorsal, and from the cerebral hemispheres to the spinal cord [50]. Several studies suggest NAA to be a brain osmolyte with possible reversible changes [51–53]. Finally, lactate is a marker of anaerobic glycolysis conditions which is at the limit of detectability in normal brain and may increase due to severe posttraumatic injury or brain hypoxia or ischemia.

To assess brain function in coma survivors, a comprehensive MRS protocol should include an axial chemical shift imaging at the level of the basal ganglia to include thalamus, insular cortex, and periventricular white matter in the field of exploration and a single-voxel 1H spectroscopy placed on the posterior two-thirds of the pons. Several investigations from the literature were promising in terms of the role of proton MRS as an accurate tool to predict patient outcome. A TBI case-control study revealed that the level of NAA/Cr ratio was correlated with recovery of patient whereas no clear link with other metabolite ratios such as Cho/Cr was observed [23]. Others showed that metabolic changes in TBI patients could be detected with MRS even in the days after the trauma [14]. Indeed, NAA was decreased and correlated with the initial GCS and the outcome at 3 months in these patients. The NAA/Cho ratio was shown to be able to disentangle patients who did not recover from those who regained consciousness [17]. Other studies have showed a significant correlation between NAA/Cr ratio and outcome of TBI patients in gray and white matter of occipito-parietal [15, 18], frontal [22], splenium of corpus callosum [19], and thalamic brain regions [20]. In addition, pons MRS recorded in the acute phase seems to allow to separate patients who recovered from patients with severe neurological impairment, death or in vegetative state [21]. Three MRS profiles of the pons could be drawn after a trauma: (1) normal profile with higher peak of NAA than Cho and Cr; (2) neuronal loss profile with a decreased NAA peak, nearly to the level of the Cr peak (the NAA/Cr ratio is 1.50 and NAA/(Cho+Cr+NAA)=0.40); (3) gliosis profile with increased Cho peak, no change in the Cr or NAA peak and Cho/Cr or NAA/Cr or Cho/(Cho+Cr+NAA)=0.40.

Finally, NAA/Cr ratio seems to be better than NAA/Cho for evaluating traumatic patients and its decrease appears to be a reliable index of unfavorable outcome [54]. Indeed, the NAA decreases within a few minutes after the traumatism and reaches its minimum within 48 h. Its level remains stable within the first month after the injury, supporting the validity of MRS assessments during the second or third week [55, 56]. Between 6 weeks and 1 year after the insult, the evolution of the NAA/Cr ratio is more heterogeneous, and NAA levels have been shown to decrease or increase. This possible variability in NAA levels is a potential limitation of this technique. In addition, the use of ratios may be problematic insofar that their common denominator is the Cr that is supposed to be stable in normal brain tissue and used to standardize other brain metabolites. However, to our knowledge, there is no evidence that Cr is invariable in TBI and it may be affected similarly to the metabolite of interest. Also, creatine MRS data can be reduced in hypermetabolic and raised in hypometabolic states [57, 58] which might bias recordings obtained in mild-traumatic-injured patients [59]. Whole brain NAA MRS and repetition of MRS examinations during the subacute phase might reduce the possible impact of NAA variability and hence improve MRS performance.

Functional magnetic resonance imaging fMRI now offers the possibility of directly measuring the brain’s activity, not only at rest or during passive stimulation, but also in response to commands [9]. Several fMRI activation studies in vegetative state (see Table 1, [60–66]) have confirmed previous $H_2{}^{15}O$ positron emission tomography (PET) studies showing preserved activation of “lower level” primary sensory cortices which are disconnected from “higher order” associative cortical networks employing both auditory [67–70], somatosensory [67, 71], or visual [70, 72] stimulations. Schiff et al. [73] were the first to perform fMRI in minimally conscious patients. They demonstrated a residual capacity to activate large integrative networks in two minimally conscious patients. Similar studies in PET reported that minimally conscious patients showed a more widespread activation than did patients in a vegetative state, with a cortico-cortical functional connectivity more efficient in minimally conscious compared to vegetative patients [68]. Moreover, stimuli with emotional valence (cries and names) were showed to induce a much more widespread activation than did meaningless noise in the minimally conscious state [74]. Such context-dependent higher-order auditory processing shows that content does matter when talking to minimally conscious patients. Exceptionally, vegetative patients may also show higher atypical level cortical activation and this was proposed to be a surrogate marker of good prognosis [75].

However, in the absence of a full understanding of the neural correlates of consciousness, even a near-to-normal activation in response to passive sensory stimulation cannot

Table 1 Functional magnetic resonance imaging (fMRI) studies in chronic disorders of consciousness.

First author [reference]	Number of patients	Diagnosis	Etiology	Interval (mean±SD)	Stimulation	Main findings
Moritz [65]	1	VS	TBI	4 days	Tactile/visual/auditory	Near-normal primary sensory cortex activation (good recovery at 3 months post-fMRI)
Schiff [73]	2	MCS	TBI/NTBI	18–24 months	Tactile/auditory	Normal "lower" and "higher" level brain activity
Eickhoff [81]	1	Coma	TBI	35 months	Auditory/visual/tactile	Near-normal primary sensory cortex activation
Bekinschtein [60]	1	VS	TBI	2 months	Auditory	Limited primary auditory cortex activation (more widespread activation after recovery)
Staffen [66]	1	VS	Anoxic	11 months	Auditory	Differential mesiofrontal activation during own name compared to other name stimulation (no recovery)
Owen [76]	1	VS	TBI	5 months	Auditory active tasks	Near-normal activation during mental imagery tasks indicating preserved command following (recovered functional communication)
Di [63]	12	7VS/5MCS	TBI/NTBI	10±14 months	Auditory	Only the 2 VS patients showing atypical "high level" cortical activation recovered to MCS 3 months after fMRI
Coleman [62]	14	7VS/5MCS/2EMCS	TBI/NTBI	26±39 months	Auditory	No relationship between fMRI responses and diagnosis of VS vs MCS. Some VS patients retain near-normal speech-processing network activation
Fernández-Espejo [64]	7	3VS/4MCS	TBI	6±3 months	Auditory	No relationship between fMRI responses and diagnosis of VS vs MCS. 1VS with near-normal speech-processing network activation recovered 9 months later. 1MCS showed no activation
Coleman [61]	41	22VS/19MCS	TBI/NTBI	18±26 months	Auditory	All VS (7) showing near-normal speech-processing network activation recover to MCS 6-months post-fMRI
Zhu [82]	9	MCS	TBI/NTBI	1–2 months	Visual–emotional	Pictures of family members elicit near-normal activation (more than non-familiar pictures)
Boly [83]	2	1VS/1 BD	NTBI	18 months/2 days	Resting state	Residual default network integrity in VS (absent in BD)
Cauda [84]	3	VS	TBI/NTBI	20 months	Resting state	Residual default network integrity

BD brain death, *VS* vegetative state, *MCS* minimally conscious state, *EMC* emergence of minimally conscious state, *TBI* traumatic brain injury, *NTBI* non-traumatic brain injury

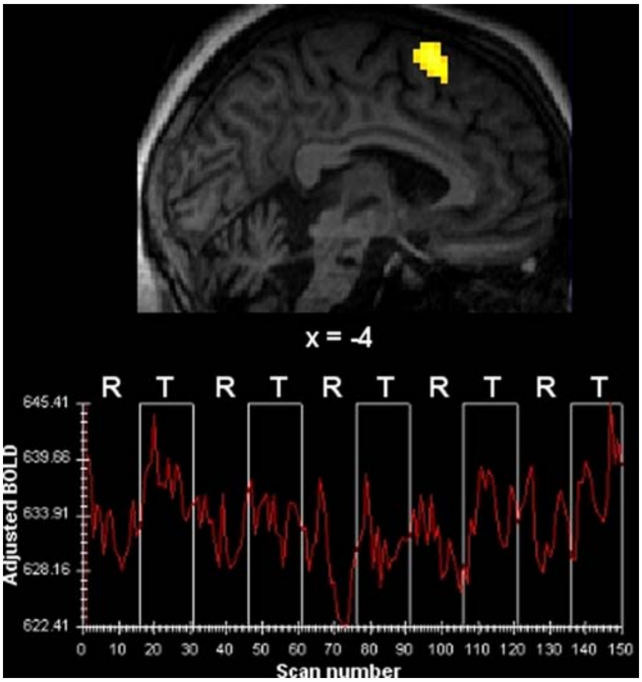


Fig. 2 Mental imagery ("play tennis") shows activation in pre-supplementary motor area in a 22-year-old locked-in syndrome patient. *T* play tennis, *R* rest (TR/TE: 2,000/30 ms, slices: 32, voxel size: 3.4×3.4×3 mm^3; Vanhaudenhuyse et al., unpublished data)

be considered as a proof of the presence of awareness in chronic disorders of consciousness patients. Instead, all that can be inferred is that a specific brain region is, to some degree, still able to process the relevant sensory stimuli. The question that arises is how can we disentangle automatic from conscious brain activation? The potential of fMRI, the best, so far, to unequivocally prove the presence of consciousness, was illustrated by the extraordinary case published by Owen et al. [76]. They reported fMRI results on a young woman in a vegetative state for 5 months following a severe TBI. When she was verbally requested to perform two ideational tasks consisting primarily to imagine playing tennis and then to imagine walking through her house, they observed fMRI activation in the same areas as the healthy controls (Fig. 2). They concluded that the patient was consciously aware of herself and her surroundings. Interestingly, she regained clinical signs of awareness 6 months later. This case illustrates that novel neuroimaging methods can now be used to detect signs of consciousness, not found during a thorough neurological examination, in non-communicative patients with brain damage. The results of this study should not be misinterpreted as evidence that all patients in a vegetative state may actually be conscious. Indeed, it should be noted

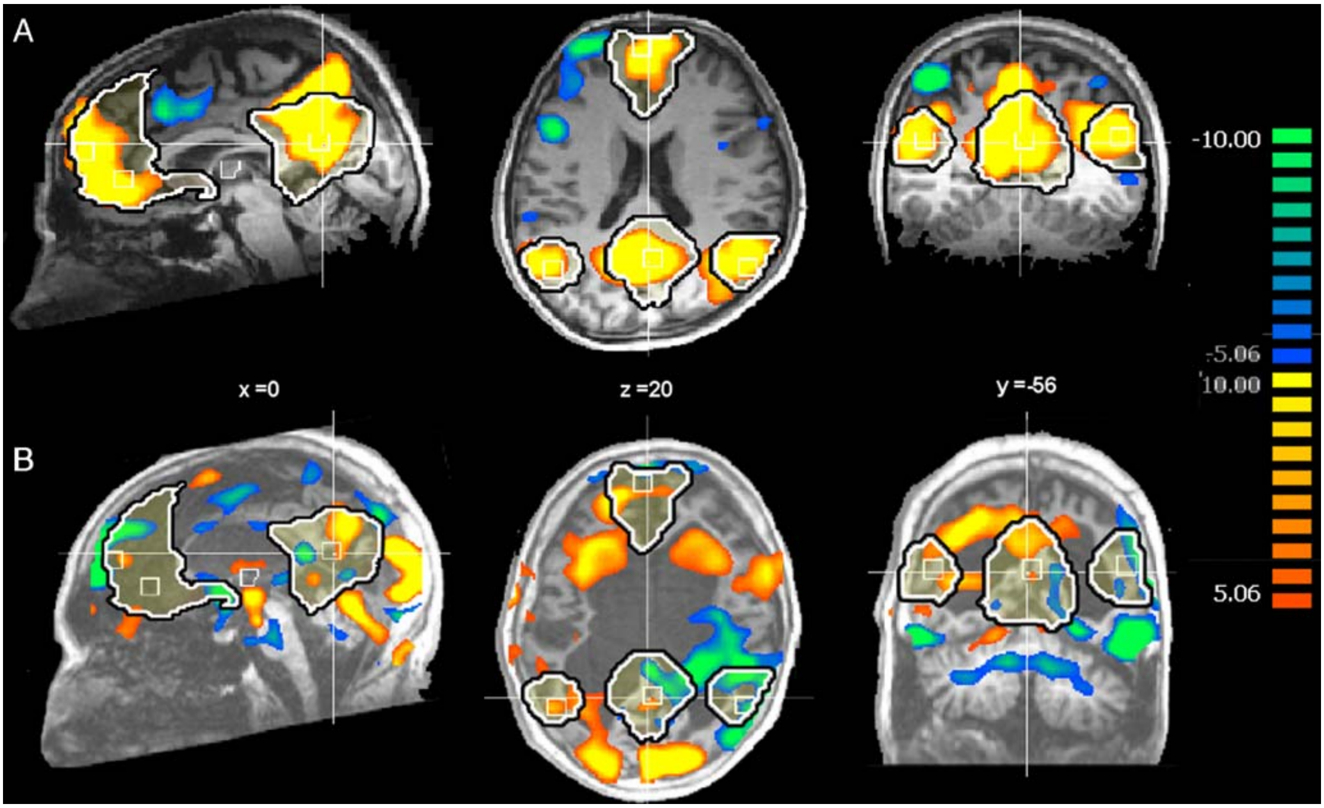


Fig. 3 Resting-state EPI acquisition in: **a** healthy volunteers illustrating the default mode network (*DMN*) in yellow encompassing mesiofrontal/anterior cingulate, precuneus/posterior cingulate and bilateral posterior parietal cortices. **b** A vegetative state patient 21 years post-anoxia, illustrating the absence of DMN connectivity (TR/TE: 2,000/30 ms, slices: 32, voxel size: 3.4×3.4×3 mm^3)

that some months after the study, the reported patient also showed behavioral signs of recovery. The most likely explanation of these results is that the patient was already beginning the transition to the minimally conscious state at the time of the experiment. This study also confirmed that fMRI could be a potentially good marker of prognosis. Active paradigm seems to provide a valuable additional diagnostic tool in cases of patients with atypical presentation, leading to persisting doubts in clinical diagnosis. Negative results, however, must be cautiously interpreted in case of patients with severely altered level of vigilance, which could present only transient activity in response to the presentation of instructions.

Resting-state fMRI acquisitions are also very easy to perform and could thus have a potentially broader and faster translation into clinical practice. Recent studies on spontaneous fluctuations in the functional MRI blood-oxygen-level-dependent (BOLD) signal recorded in “resting” awake healthy subjects showed the presence of coherent fluctuations among functionally defined neuroanatomical networks [77, 78]. The concept of “default mode network” (DMN) of brain function was proposed by Raichle et al. [79] to describe a number of brain regions encompassing the precuneus, posterior parietal lobe, and medial prefrontal cortex which are more active at rest than when we are involved in attention-demanding cognitive tasks (Fig. 3). The clinical interest of DMN MRI studies is that it allows the investigation of higher-order cognitive networks, without requiring patients’ collaboration, particularly important in vegetative and minimally conscious patients. Recently, Boly et al. [80, 83] showed that some slow coherent BOLD fluctuations characteristic of the DMN in healthy subjects can be found in vegetative patients and not in brain death, and are thus unlikely to be uniquely due to ongoing modifications of conscious thoughts. While these results are very preliminary, this technique may be interesting to test the functional integrity of major brain structures and could be useful to distinguish unconscious–vegetative from conscious–minimally conscious patients. However, future studies are needed to give a full characterization of DMN connectivity in VS and MCS patients and its potential use in outcome prediction.

Conclusion

Assessing consciousness in coma survivors who remain unable to express (verbally or non-verbally) their thoughts and feelings is difficult by means of behavioral observation only. At present, MRI is the procedure of choice for the structural and functional imaging of the brain. While sequences such as DTI and MRS seems promising to reliably predict outcome in chronic disorders patients with severe TBI; passive, active, and resting-state functional neuroimaging paradigms are currently being validated to help in differentiating unconscious–vegetative from minimally conscious patients. These scientific progresses in neuroimaging, and its potential clinical translation, presents an opportunity to better meet the needs of these patients and provide families with better diagnostic and prognostic information. The major challenges of these acquisitions are patient selection, study design, and standardization of protocol (e.g., stimulus selection). Their susceptibility to movement artifacts and patients who are on life support systems or who have implanted MRI-incompatible material (pacemakers, prostheses, etc.) still remain problematic. Ongoing refinements for a wise use of these powerful tools and the information they produce can aid our understanding and management of chronic disorders of consciousness.

Acknowledgments This research was supported by the Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge, DECODER & CATIA), Concerted Research Action (ARC-06/11-340), McDonnell Foundation, Mind Science Foundation. The authors thank the technicians of the Department of Neuroradiology of the Centre Hospitalier Universitaire, Liege, for their active participation in the MRI studies in comatose patients.

Conflict of interest statement We declare that we have no conflict of interest.

References

1. Laureys S, Boly M (2008) The changing spectrum of coma. Nat Clin Pract Neurol 4(10):544–546
2. Posner J, Saper C, Schiff N, Plum F (2007) Plum and Posner's diagnosis of stupor and coma. Oxford University Press, New York
3. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (1). N Engl J Med 330(21):1499–1508
4. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND (2002) The minimally conscious state: definition and diagnostic criteria. Neurology 58(3):349–353
5. American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. Arch Phys Med Rehabil 76:205–209
6. Andrews K, Murphy L, Munday R, Littlewood C (1996) Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 313(7048):13–16
7. Childs NL, Mercer WN (1996) Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs [letter; comment]. BMJ 313(7062):944
8. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S (2009) Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 9:35
9. Giacino JT, Hirsch J, Schiff N, Laureys S (2006) Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. Arch Phys Med Rehabil 87(12 Suppl):67–76

10. Parvizi J, Damasio A (2001) Consciousness and the brainstem. Cognition 79(1–2):135–160
11. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, Franck G, Maquet P (1999) Impaired effective cortical connectivity in vegetative state. Neuroimage 9(4):377–382
12. Weiss N, Galanaud D, Carpentier A, Naccache L, Puybasset L (2007) Clinical review: prognostic value of magnetic resonance imaging in acute brain injury and coma. Crit Care 11(5):230
13. Huisman TA, Schwamm LH, Schaefer PW, Koroshetz WJ, Shetty-Alva N, Ozsunar Y, Wu O, Sorensen AG (2004) Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am J Neuroradiol 25(3):370–376
14. Marino S, Zei E, Battaglini M, Vittori C, Buscalferri A, Bramanti P, Federico A, De Stefano N (2007) Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. J Neurol Neurosurg Psychiatry 78(5):501–507
15. Ross BD, Ernst T, Kreis R, Haseler LJ, Bayer S, Danielsen E, Bluml S, Shonk T, Mandigo JC, Caton W, Clark C, Jensen SW, Lehman NL, Arcinue E, Pudenz R, Shelden CH (1998) 1H MRS in acute traumatic brain injury. J Magn Reson Imaging 8(4):829–840
16. Trivedi MA, Ward MA, Hess TM, Gale SD, Dempsey RJ, Rowley HA, Johnson SC (2007) Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. J Neurotrauma 24(5):766–771
17. Ricci R, Arbarella G, Musi P, Oldrini P, Revisan C, Asaglia N (1997) Localised proton MR spectroscopy of brain metabolism changes in vegetative patients. Neuroradiology 39:313–319
18. Friedman SD, Brooks WM, Jung RE, Chiulli SJ, Sloan JH, Montoya BT, Hart BL, Yeo RA (1999) Quantitative proton MRS predicts outcome after traumatic brain injury. Neurology 52(7):1384–1391
19. Sinson G, Bagley LJ, Cecil KM, Torchia M, McGowan JC, Lenkinski RE, McIntosh TK, Grossman RI (2001) Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: correlation with clinical outcome after traumatic brain injury. AJNR Am J Neuroradiol 22(1):143–123
20. Uzan M, Albayram S, Dashti SG, Aydin S, Hanci M, Kuday C (2003) Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. J Neurol Neurosurg Psychiatry 74(1):33–38
21. Carpentier A, Galanaud D, Puybasset L, Muller JC, Lescot T, Boch AL, Riedl V, Cornu P, Coriat P, Dormont D, van Effenterre R (2006) Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". J Neurotrauma 23(5):674–685
22. Garnett MR, Blamire AM, Corkill RG, Cadoux-Hudson TA, Rajagopalan B, Styles P (2000) Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. Brain 123(Pt 10):2046–2054
23. Choe BY, Suh TS, Choi KH, Shinn KS, Park CK, Kang JK (1995) Neuronal dysfunction in patients with closed head injury evaluated by in vivo 1H magnetic resonance spectroscopy. Invest Radiol 30(8):502–506
24. Tollard E, Galanaud D, Perlbarg V, Sanchez-Pena P, Le Fur Y, Abdennour L, Cozzone P, Lehericy S, Chiras J, Puybasset L (2009) Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: preliminary results. Crit Care Med 37(4):1448–1455
25. Gerber DJ, Weintraub AH, Cusick CP, Ricci PE, Whiteneck GG (2004) Magnetic resonance imaging of traumatic brain injury: relationship of T2*SE and T2GE to clinical severity and outcome. Brain Inj 18(11):1083–1097
26. Scheid R, Preul C, Gruber O, Wiggins C, von Cramon DY (2003) Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3 T. AJNR Am J Neuroradiol 24(6):1049–1056
27. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1(7905):480–484
28. Yanagawa Y, Tsushima Y, Tokumaru A, Un-no Y, Sakamoto T, Okada Y, Nawashiro H, Shima K (2000) A quantitative analysis of head injury using T2*-weighted gradient-echo imaging. J Trauma 49(2):272–277
29. Levin HS, Mendelsohn D, Lilly MA, Yeakley J, Song J, Scheibel RS, Harward H, Fletcher JM, Kufera JA, Davidson KC, Bruce D (1997) Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the Ommaya–Gennarelli model. Neurosurgery 40(3):432–441 discussion 440–431
30. Kampfl A, Schmutzhard E, Franz G, Pfausler B, Haring HP, Ulmer H, Felber S, Golaszewski S, Aichner F (1998) Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. Lancet 351(9118):1763–1767
31. Kampfl A, Franz G, Aichner F, Pfausler B, Haring HP, Felber S, Luz G, Schocke M, Schmutzhard E (1998) The persistent vegetative state after closed head injury: clinical and magnetic resonance imaging findings in 42 patients. J Neurosurg 88(5):809–816
32. Firsching R, Woischneck D, Diedrich M, Klein S, Ruckert A, Wittig H, Dohring W (1998) Early magnetic resonance imaging of brainstem lesions after severe head injury. J Neurosurg 89(5):707–712
33. Wedekind C, Fischbach R, Pakos P, Terhaag D, Klug N (1999) Comparative use of magnetic resonance imaging and electrophysiologic investigation for the prognosis of head injury. J Trauma 47 (1):44–49
34. Hoelper BM, Soldner F, Chone L, Wallenfang T (2000) Effect of intracerebral lesions detected in early MRI on outcome after acute brain injury. Acta Neurochir Suppl 76:265–267
35. Paterakis K, Karantanas AH, Komnos A, Volikas Z (2000) Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. J Trauma 49(6):1071–1075
36. Karantanas A, Paterakis K (2000) Magnetic resonance imaging and brainstem injury. J Neurosurg 92(5):896–897
37. Schaefer PW, Huisman TA, Sorensen AG, Gonzalez RG, Schwamm LH (2004) Diffusion-weighted MR imaging in closed head injury: high correlation with initial glasgow coma scale score and score on modified Rankin scale at discharge. Radiology 233(1):58–66
38. Galanaud D, Naccache L, Puybasset L (2007) Exploring impaired consciousness: the MRI approach. Curr Opin Neurol 20(6):627–631
39. Weiss N, Galanaud D, Carpentier A, Tezenas de Montcel S, Naccache L, Coriat P, Puybasset L (2008) A combined clinical and MRI approach for outcome assessment of traumatic head injured comatose patients. J Neurol 255(2):217–223
40. Huisman TA, Loenneker T, Barta G, Bellemann ME, Hennig J, Fischer JE, Il'yasov KA (2006) Quantitative diffusion tensor MR imaging of the brain: field strength related variance of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) scalars. Eur Radiol 16(8):1651–1658
41. Jones DK, Dardis R, Ervine M, Horsfield MA, Jeffree M, Simmons A, Jarosz J, Strong AJ (2000) Cluster analysis of diffusion tensor magnetic resonance images in human head injury. Neurosurgery 47(2):306–313 discussion 313–304
42. Huisman TA, Sorensen AG, Hergan K, Gonzalez RG, Schaefer PW (2003) Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. J Comput Assist Tomogr 27(1):5–11
43. Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME (2002) Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am J Neuroradiol 23(5):794–802
44. Xu J, Rasmussen IA, Lagopoulos J, Haberg A (2007) Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J Neurotrauma 24 (5):753–765
45. Filippi CG, Ulug AM, Ryan E, Ferrando SJ, van Gorp W (2001) Diffusion tensor imaging of patients with HIV and normal-

appearing white matter on MR images of the brain. AJNR Am J Neuroradiol 22(2):277–283

46. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2(7872):81–84
47. Perlbarg V, Puybasset L, Tollard E, Lehericy S, Benali H, Galanaud D (2009) Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. Hum Brain Mapp in press
48. Voss HU, Uluc AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, Heier LA, Beattie BJ, Hamacher KA, Vallabhajosula S, Goldsmith SJ, Ballon D, Giacino JT, Schiff ND (2006) Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest 116(7):2005–2011
49. Cecil KM, Hills EC, Sandel ME, Smith DH, McIntosh TK, Mannon LJ, Sinson GP, Bagley LJ, Grossman RI, Lenkinski RE (1998) Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. J Neurosurg 88(5):795–801
50. Pouwels PJ, Frahm J (1998) Regional metabolite concentrations in human brain as determined by quantitative localized proton MRS. Magn Reson Med 39(1):53–60
51. Baslow MH, Hrabe J, Guilfoyle DN (2007) Dynamic relationship between neurostimulation and N-acetylaspartate metabolism in the human visual cortex: evidence that NAA functions as a molecular water pump during visual stimulation. J Mol Neurosci 32(3):235–245
52. Baslow MH, Suckow RF, Gaynor K, Bhakoo KK, Marks N, Saito M, Saito M, Duff K, Matsuoka Y, Berg MJ (2003) Brain damage results in down-regulation of *N*-acetylaspartate as a neuronal osmolyte. Neuromolecular Med 3(2):95–104
53. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM (2007) *N*-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol 81(2):89–131
54. Cecil KM, Lenkinski RE, Meaney DF, McIntosh TK, Smith DH (1998) High-field proton magnetic resonance spectroscopy of a swine model for axonal injury. J Neurochem 70(5):2038–2044
55. Holshouser BA, Tong KA, Ashwal S, Oyoyo U, Ghamsary M, Saunders D, Shutter L (2006) Prospective longitudinal proton magnetic resonance spectroscopic imaging in adult traumatic brain injury. J Magn Reson Imaging 24(1):33–40
56. Signoretti S, Marmarou A, Fatouros P, Hoyle R, Beaumont A, Sawauchi S, Bullock R, Young H (2002) Application of chemical shift imaging for measurement of NAA in head injured patients. Acta Neurochir Suppl 81:373–375
57. Castillo M, Kwock L, Mukherji SK (1996) Clinical applications of proton MR spectroscopy. AJNR Am J Neuroradiol 17(1):1–15
58. Wood SJ, Berger G, Velakoulis D, Phillips LJ, McGorry PD, Yung AR, Desmond P, Pantelis C (2003) Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. Schizophr Bull 29(4):831–843
59. Lewine JD, Davis JT, Sloan JH, Kodituwakku PW, Orrison WW Jr (1999) Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma. AJNR Am J Neuroradiol 20(5):857–866
60. Bekinschtein T, Tiberti C, Niklison J, Tamashiro M, Carpintiero S, Villarreal M, Forcato C, Leiguarda R, Manes F (2005) Assessing level of consciousness and cognitive changes from vegetative state to full recovery. Neuropsychol Rehabil 15(3/4):307–322
61. Coleman MR, Davis MH, Rodd JM, Robson T, Ali A, Owen AM, Pickard JD (2009) Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 132(Pt 9):2541–2552
62. Coleman MR, Rodd JM, Davis MH, Johnsrude IS, Menon DK, Pickard JD, Owen AM (2007) Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain 130(10):2494–2507
63. Di HB, Yu SM, Weng XC, Laureys S, Yu D, Li JQ, Qin PM, Zhu YH, Zhang SZ, Chen YZ (2007) Cerebral response to patient's own name in the vegetative and minimally conscious states. Neurology 68(12):895–899
64. Fernandez-Espejo D, Junque C, Vendrell P, Bernabeu M, Roig T, Bargallo N, Mercader JM (2008) Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. Brain Inj 22(11):882–890
65. Moritz CH, Rowley HA, Haughton VM, Swartz KR, Jones J, Badie B (2001) Functional MR imaging assessment of a non-responsive brain injured patient. Magn Reson Imaging 19 (8):1129–1132
66. Staffen W, Kronbichler M, Aichhorn M, Mair A, Ladurner G (2006) Selective brain activity in response to one's own name in the persistent vegetative state. J Neurol Neurosurg Psychiatry 77 (12):1383–1384
67. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas F, Luxen A, Lamy M, Moonen G, Maquet P, Laureys S (2005) Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS. Neuropsychol Rehabil 15(3–4):283–289
68. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas P, Del Fiore G, Degueldre C, Franck G, Luxen A, Lamy M, Moonen G, Maquet P, Laureys S (2004) Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 61 (2):233–238
69. Laureys S, Faymonville ME, Degueldre C, Fiore GD, Damas P, Lambermont B, Janssens N, Aerts J, Franck G, Luxen A, Moonen G, Lamy M, Maquet P (2000) Auditory processing in the vegetative state. Brain 123(8):1589–1601
70. Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, Williams EJ, Mummery C, Pickard JD (2002) Detecting residual cognitive function in persistent vegetative state. Neurocase 8 (5):394–403
71. Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, Lancellotti P, Luxen A, Lamy M, Moonen G, Maquet P, Laureys S (2008) Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 7:1013–20
72. Menon DK, Owen AM, Williams EJ, Minhas PS, Allen CM, Boniface SJ, Pickard JD (1998) Cortical processing in persistent vegetative state. Lancet 352(9123):200
73. Schiff ND, Rodriguez-Moreno D, Kamal A, Kim KH, Giacino JT, Plum F, Hirsch J (2005) fMRI reveals large-scale network activation in minimally conscious patients. Neurology 64(3):514–523
74. Laureys S, Perrin F, Faymonville ME, Schnakers C, Boly M, Bartsch V, Majerus S, Moonen G, Maquet P (2004) Cerebral processing in the minimally conscious state. Neurology 63(5):916–918
75. Di H, Boly M, Weng X, Ledoux D, Laureys S (2008) Neuroimaging activation studies in the vegetative state: predictors of recovery? Clin Med 8(5):502–507
76. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD (2006) Detecting awareness in the vegetative state. Science 313(5792):1402
77. Raichle ME (2006) Neuroscience. The brain's dark energy. Science 314(5803):1249–1250
78. Boly M, Phillips C, Tshibanda L, Vanhaudenhuyse A, Schabus M, Dang-Vu TT, Moonen G, Maquet P, Laureys S (2008) Intrinsic brain activity in altered states of consciousness. How conscious is the default mode of brain function? Ann N Y Acad Sci 1129:119–129
79. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98(2):676–682
80. Boly M, Phillips C, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Peigneux P, Faymonville ME, Maquet P,

Laureys S (2008) Consciousness and cerebral baseline activity fluctuations. Hum Brain Mapp 29(7):868–874

81. Eickhoff SB, Dafotakis M, Grefkes C, Stocker T, Shah NJ, Schnitzler A, Zilles K, Siebler M (2008) fMRI reveals cognitive and emotional processing in a long-term comatose patient. Exp Neurol 214(2):240–246
82. Zhu J, Wu X, Gao L, Mao Y, Zhong P, Tang W, Zhou L (2009) Cortical activity after emotional visual stimulation in minimally conscious state patients. J Neurotrauma 26(5):677–688
83. Boly M, Tshibanda L, Vanhaudenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, Boveroux P, Garweg C, Lambermont B, Phillips C, Luxen A, Moonen G, Bassetti C, Maquet P, Laureys S (2009) Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum Brain Mapp 30(8):2393–2400
84. Cauda F, Micon BM, Sacco K, Duca S, D'Agata F, Geminiani G, Canavero S (2009) Disrupted intrinsic functional connectivity in the vegetative state. J Neurol Neurosurg Psychiatry 80(4):429–431

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123
Copyright © 2009 Elsevier B.V. All rights reserved

CHAPTER 15

Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls☆

Luaba Tshibanda[1,2], Audrey Vanhaudenhuyse[1], Damien Galanaud[3], Mélanie Boly[1], Steven Laureys[1,*] and Louis Puybasset[4]

[1]*Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Belgium*
[2]*Department of Neuroradiology, University Hospital of Liège, Belgium*
[3]*Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France*
[4]*Department of Anesthesiology-Reanimation, Pitié-Salpêtrière Hospital, Paris, France*

Abstract: The status of comatose patient is currently established on the basis of the patient-exhibited behaviors. Clinical assessment is subjective and, in 40% of patients, fails to distinguish vegetative state (VS) from minimally conscious states (MCS). The technologic advances of magnetic resonance imaging (MRI) have dramatically improved our understanding of these altered states of consciousness. The role of neuroimaging in coma survivors has increased beyond the simple evaluation of morphological abnormalities. The development of 1H-MR spectroscopy (MRS) and diffusion tensor imaging (DTI) provide opportunity to evaluate processes that cannot be approached by current morphologic MRI sequences. They offer potentially unique insights into the histopathology of VS and MCS. The MRS is a powerful noninvasive imaging technique that enables the in vivo quantification of certain chemical compound or metabolites as N-acetylaspartate (NAA), Choline (Cho), and Creatine (Cr). These biomarkers explore neuronal integrity (NAA), cell membrane turnover (Cho), and cell energetic function (Cr). DTI is an effective and proved quantitative method for evaluating tissue integrity at microscopic level. It provides information about the microstructure and the architecture of tissues, especially the white matter. Various physical parameters can be extracted from this sequence: the fractional anisotropy (FA), a marker of white matter integrity; mean diffusivity (MD); and the apparent diffusion coefficient (ADC) which can differentiate cytotoxic and vasogenic edema. The most prominent findings with MRS and DTI performed in traumatic brain-injured (TBI) patients in subacute phase are the reduction of the NAA/Cr ratio in posterior pons and the decrease of mean infratentorial and supratentorial FA except in posterior pons that enables to predict unfavorable outcome at 1 year from TBI with up to 86% sensitivity and 97% specificity. This review will focus on the interest of comatose patients MRI multimodal assessment with

---

☆ Luaba Tshibanda and Audrey Vanhaudenhuyse contributed equally to this work.

*Corresponding author.
Tel.: +32 4 366 23 16; Fax: +32 4 366 29 46;
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17715-4

MRS and DTI. It will emphasize the advantages and pitfalls of these techniques in particular in predicting the coma survivors' outcome.

Keywords: traumatic brain injury; coma; diffusion tensor imaging; spectroscopy; prognosis; outcome

Introduction

Survivors of severe brain damage following traumatic brain injury (TBI), stroke, or anoxic/hypoxic encephalopathy may remain in an altered state of consciousness during several years. TBI is the most frequent etiology of severe brain damage among young and middle-aged adults (as compared to stroke and tumors in elderly subjects; Katz, 1997), leading to up to 14% of subsequently permanently vegetative patients (Celesia, 1993; Jennett, 2005; Payne et al., 1996). However, in about 5–10% of these TBI patients, anatomical lesions detected by classical morphological MRI (sequences such as T2*, FLAIR, and diffusion) are unable to explain their clinical status and to give clue about their chance of recovery. These patients present significant problems concerning diagnosis and misdiagnosis, prognosis, and therapy (Andrews et al., 1996; Childs and Mercer, 1996; Schnakers et al., 2009). The announcement of an optimistic outcome will increase the commitment of the team, while a pessimistic prognosis risks demobilizing and jeopardizing the potential recovery of the patient. Questions about end of life, aggressive therapy, limitation of care, and euthanasia often arise in such cases and lead to passionate debates among the medical staff, and sometimes more widely in the media and society. Therefore, neuroimaging techniques should be used not only to evaluate structural abnormality and detect TBI complications but also to reliably show the extent of brain damage in a clinical diagnostic and a therapeutic way and lead to a better understanding of the behavioral observations. In this review, we discuss recent developments in the use of proton magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) in the assessment of brain injury patients in particular after TBI due to the frequency of this etiology.

Imaging protocols

Magnetic resonance imaging (MRI) in coma survivors is routinely performed on 1.5 T or 3 T MR scanners. MRI assessment may often be limited by patient motion which can necessitate sedation; the risk of uncontrolled intracranial pressure occurring during the exam if performed when brain swelling is still present; unstable hemodynamic or respiratory condition, due to the limited monitoring available in the magnet; and artifacts generated by some metallic devices (most commonly intracranial pressure valves). In our view, a comprehensive patient MRI exploration should check both infra- and supratentorial structures, involved in arousal and awareness functions (Boly et al., 2008b). The ascending reticular activating system, located in the posterior part of the upper two-thirds of the brainstem is the primary arousal structure (Parvizi and Damasio, 2001; Plum and Posner, 1980). The evaluation of the patient's brain ability to generate awareness should include the assessment of the integrity of a large set of supratentorial structures, encompassing thalamus, basal forebrain, and fronto-parietal association cortices (Laureys et al., 1999; Parvizi and Damasio, 2001; Selden et al., 1998).

Classical morphological MRI was shown to poorly correlate with recovery of consciousness in severely brain-damaged patients. The fact that patients often develop progressive posttraumatic global brain atrophy (Table 1), despite the fact that initial morphologic imaging revealed only discrete findings or failed to show any pathology, also reflects the insufficiency of conventional imaging techniques to comprehensively evaluate the gravity of brain lesion in individual patients (Anderson et al., 1996; Gale et al., 1995; Gentry et al., 1988; Kelly et al., 1988). In particular, morphological MRI is not accurate for diagnosis

Table 1. Prognosis values of structural magnetic resonance imaging, magnetic resonance spectroscopy, diffusion weighted imaging and diffusion tensor imaging in altered state of consciousness patients

Authors	Number of patients	Diagnosis	Etiology	Interval	Main findings
Structural magnetic resonance imaging					
Firsching et al. (1998)	61	Coma; CGS ≤ 7 ($n = 61$)	TBI	<7 d	100% of mortality with bilateral pontine lesion, 2% with no brainstem lesion, 8% with unilateral or midline mesencephalon lesion, 8% with unilateral pons or medulla oblongata lesion, and 0% with lesion of the lower bilateral portions of medulla oblongata
Kampfl et al. (1998)	80	Vegetative state; CGS ≤ 8 ($n = 80$)	TBI	50 d, range 42–56	214-fold higher probability for not recovering with lesions in the corpus callosum and 7-fold with dorsolateral brainstem lesion
Paterakis et al. (2000)	24	Severe head injury; GCS < 8 ($n = 19$); Moderate head injury; GCS 9–12 ($n = 5$)	TBI	<48 h	Good recovery when hemorrhagic DAI lesions; unfavorable outcome not associated with isolated nonhemorrhagic DAI lesions; 100% of unfavorable outcome when subcortical gray matter injury; subarachnoid hemorrhage not associated with favorable and unfavorable outcome
Carpentier et al. (2006)	40	Severe TBI; GCS 6 ± 3 ($n = 40$)	TBI	17 ± 11 d	Number of brainstem lesions: 4.3 ± 3.3 for patients with GOS = 1–2, 1.9 ± 1.5 for GOS = 3, 0.5 ± 1.1 for GOS = 4–5
Magnetic resonance spectroscopy					
Choe et al. (1995)	10	Closed head injury; GCS 3–12 ($n = 10$)	TBI	132 ± 134 d	Fronto-parietal white matter: positive correlation of NAA/Cr ratio with emergence of vegetative state
Friedman et al. (1999)	14	TBI; GCS 3–8 ($n = 7$), GCS 9–14 ($n = 5$), GCS NA ($n = 2$)	TBI	45 ± 21 d	Occipito-parietal white and gray matter: patients with decreased NAA concentration have poor overall cognitive function at outcome
Garnett et al. (2000)	26	TBI; GCS 3–8 ($n = 9$), GCS 9–15 ($n = 17$)	TBI	12 d, range 3–35	Frontal white matter: GOS correlated with NAA/Cr ($r = 0.65$) and NAA/Cho ratio ($r = 0.58$); GOS did not correlate with Cho/Cr and Ins/Cr
Sinson et al. (2001)	30	TBI; GCS 3–15 ($n = 30$)	TBI	41 d, range 2–1129	Splenium: NAA/Cr ratio significantly lower in patients with $\leq$GOS = 1–4 (1.24 ± 0.28 NAA/Cr ratio) than GOS = 5 (1.53 ± 0.37 NAA/Cr ratio)
Uzan et al. (2003)	14	Vegetative state; GCS 4–7 ($n = 14$)	TBI	193 ± 19 d	Thalamus: lower NAA/Cr ratio in permanent vegetative patients (1.17 ± 0.25) than patients who recovered (1.8 ± 0.26, $p < 0.001$); Cho/Cr ratio did not permit outcome differentiation
Carpentier et al. (2006)	40	Severe TBI; GCS 6 ± 3 ($n = 40$)	TBI	17 ± 11 d	Brainstem: NAA/Cr ratio showed significant difference between patients with GOS = 1–2 (1.68 ± 0.4 NAA/Cr ratio) and GOS = 4–5 (2.1 ± 0.3 NAA/Cr ratio)
Marino et al. (2007)	10	TBI; GCS 4–7 ($n = 7$), GCS 8–13 ($n = 3$)	TBI	48–72 h	Central brain: correlation of GOS with NAA ($r = -0.79$) and La ratio ($r = 0.79$)

Table 1. (*Continued*)

Authors	Number of patients	Diagnosis	Etiology	Interval	Main findings
Tollard et al. (2009)	43	Closed-head injury, GCS≤7 ($n = 43$)	TBI	24±11 d	Thalamus, lenticular nucleus, insular cortical gray matter, occipital white matter: NAA/Cr values at all sites lowest in patients with GOS = 1–3 (1.3±0.3 NAA/Cr ratio) than with GOS = 4–5 (1.7±0.4 NAA/Cr ratio)
Diffusion weighted imaging					
Schaefer (2004)	26	Closed head injury; GCS 10±3 ($n = 26$)	TBI	<48 h	Correlation between number of lesions and outcome ($r = 0.662$); corpus callosum and outcome ($r = 0.513$); brainstem lesion and outcome ($r = 0.316$); basal ganglia/thalamus and outcome ($r = 0.179$)
Diffusion tensor imaging					
Huisman et al. (2004)	20	Head traumatic injury; GCS 9±4 ($n = 20$)	TBI	<7 d	Splenium: correlation between outcome and ADC ($r = -0.599$), and outcome and FA ($r = -0.694$); internal capsule: correlation between outcome and FA ($r = -0.714$), no correlation between outcome and ADC ($r = -0.018$); thalamus/putamen: no correlation between outcome and FA and ADC
Tollard et al. (2009	43	Closed head injury; GCS≤7 ($n = 43$)	TBI	24±11 d	Pons, midbrain, temporal and occipital white matter, internal and external capsules, semioval center: FA significantly lower in patients with GOS 1–3 than with GOS 4–5 patients, except in the posterior pons; 86% sensitivity and 97% specificity for predicting outcome by combining MRS and DTI analysis
Perlbarg et al. (2009)	30	TBI with persistent disorder of consciousness; GCS 6±4 ($n = 30$)	TBI	24±11 d	FA significantly lower in GOS 1–3 than in GOS 4–5 and controls in right inferior longitudinal fasciculus, right cerebral peduncle, right posterior limb of the internal capsule and posterior corpus callosum

Notes: GCS, Glasgow Coma Scale; TBI, traumatic brain injury; NA, not available; d, days; h, hours; DAI, diffuse axonal injury; NAA, N-acetylaspartate; Cr, creatinine; Cho, choline; Ins, myo-inositol; GOS, Glasgow Outcome Scale; La, lactate; ADC, apparent diffusion coefficient; FA, fractional anisotropy.

or assessment of severity and extension of diffuse axonal injury (DAI). DAI consists in diffuse white matter damage, usually caused by the effect of brutal acceleration–deceleration and/or rotational forces; resulting in stretching, disruption, and separation of axons as the brain moves inside the skull and causing important morbidity and mortality (Adams et al., 1982; Strich, 1961; Gean, 1994; Murray et al., 1996). Morphological MRI assessments were however shown to be more sensitive and specific to assess the recovery of consciousness than computed tomodensitometry and electrophysiological tools (Wedekind et al., 1999).

Taking into account these considerations, conventional MRI cannot be considered as a reliable technique to assess brain-injured patients and predict their functional outcome. The lack of sensitivity of conventional MRI led to introduce new tools in the clinical assessment of comatose

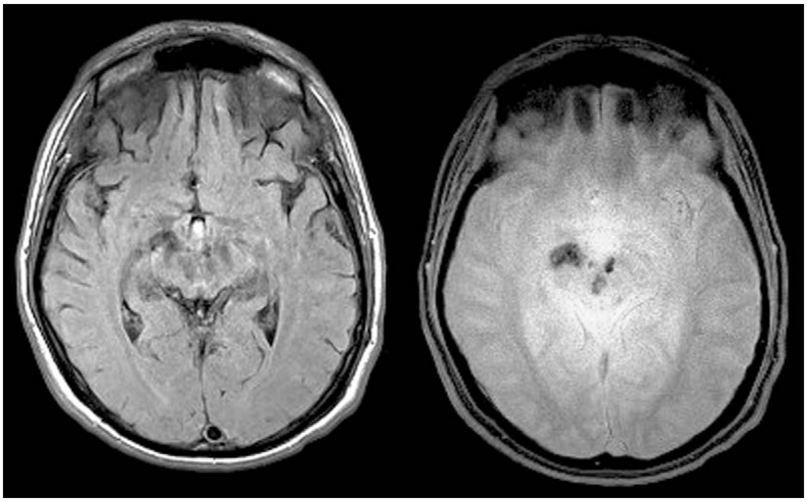


Fig. 1. Axial fluid attenuated inversion recovery (FLAIR) (left) and T2* (right) in a TBI minimally conscious patient. T2* sequence shows hyposignal in the midbrain suggestive of bleeding not clearly seen on FLAIR sequence.

patients such as positron emission tomography (PET; Beuthien-Baumann et al., 2003; Boly et al., 2008a; Laureys et al., 1999), functional MRI (fMRI; Boly et al., 2008b, Monti et al., 2009; Coleman et al., 2007; Owen et al., 2006), MRS (Cox, 1996), and DTI (Assaf and Pasternak, 2008; Voss et al. 2006). Preliminary studies suggest that these alternative functional and metabolic imaging methods could be more sensitive to detect brain damage immediately following TBI, and could thus be useful to monitoring longitudinal changes in brain function of non-communicative brain-damaged patients. In the future, they could play a crucial role in coma assessment, adding to a purely morphology-based imaging approach a more comprehensive evaluation of the patient's brain ability to generate consciousness, combining information on structure and function.

Conventional MRI protocol

In our view, in order to perform a comprehensive assessment of structural damage in individual coma patients, the morphologic MRI acquisitions should include noncontrast-enhanced sagittal T1, axial fluid attenuated inversion recovery (FLAIR), axial T2*, axial diffusion, coronal T2 sequences, and a 3D T1 weighted volume acquisition. In our centers, images are typically obtained with a section thickness of 5 mm (except for the 3D T1 which is millimetric). FLAIR sequence detects brain edema and contusion, epidural or subdural hematoma, subarachnoid hemorrhage, as well as the resulting herniation or hydrocephalus; while gradient echo-planar T2* weighted images are useful in detecting hemorrhage (Gerber et al., 2004; Scheid et al., 2003) (Fig. 1). The 3D T1 sequence provides information on the volume of the brain, and can be use during the follow up of patients. Indeed, severe and irreversible brain damage would lead to progressive brain atrophy, over a period of weeks to years (Trivedi et al., 2007).

Diffusion tensor imaging protocol

DTI is one of the most popular MRI techniques investigated in current brain-imaging research (Fig. 2). It is an extension of diffusion-weighted imaging (DWI) which is based on the principle that water molecule movement is restricted by barriers to diffusion in the brain depending on tissue organization. The acquisition protocol, image processing, analysis, and interpretation of DTI are now routinely performed in clinical conditions although it suffers from inherent

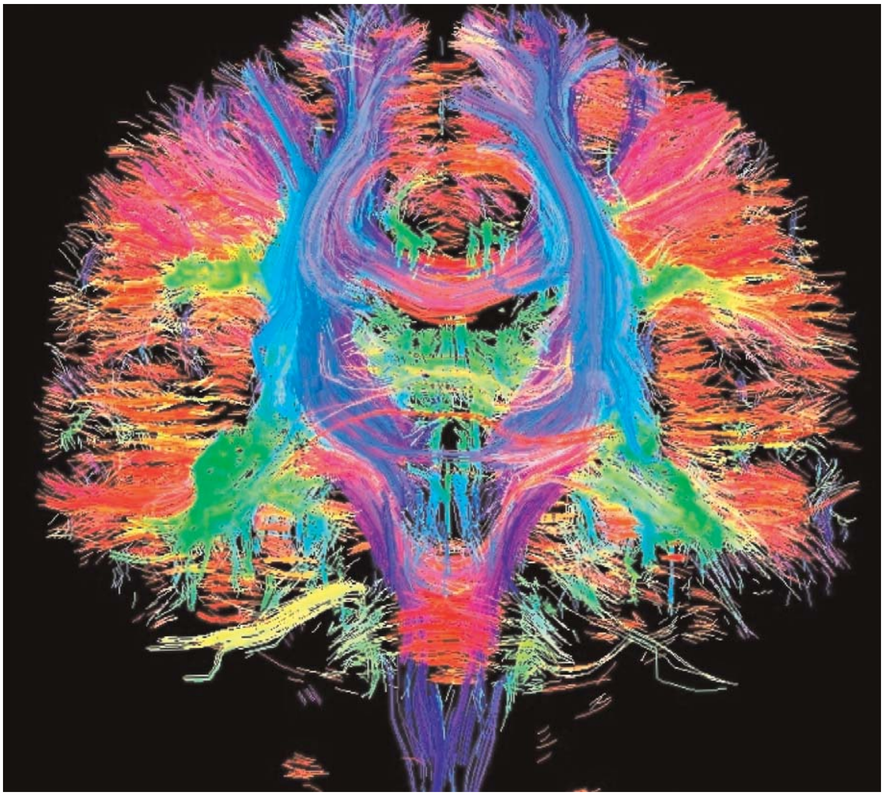


Fig. 2. Example of diffusion tensor imaging (DTI) obtained in a healthy volunteer, visualising the white matter tracts. Acquisition time: 4:51; TR/TE: 5700/90 ms; Resolution: 128 × 128; Slices: 40 transversal slices (2.0 mm thickness, 30% gap, interleaved); Voxel size: $1.8 \times 1.8 \times 2.0\,\text{mm}^3$; FoV: $230 \times 230\,\text{mm}^2$.

artifacts and limitations such as the partial volume effect and the inability of the model to cope with non-Gaussian diffusion. DTI imaging is classically performed in axial plane, using the following parameters: TR/TE, 8000/84.9 ms; 23 directions; diffusion b value, $700\,\text{s/mm}^2$; slice thickness, 5 mm; no gap; 20 slices; field of view, 32 × 32 cm; matrix, 128 × 128; and 2 averages (Tollard et al., 2009). DTI provides data that can be used to compute two basic properties: the overall amount of diffusion represented by the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA) which enable visualization and characterization of white matter (WM) in two and three dimensions. The FA characterizes the anisotropic component, that is, degree and directionality of water diffusion. Determination of FA allows a quantification of WM density in vivo and gives information about its integrity (Liu et al., 1999; Melhem et al., 2000; Pierpaoli et al., 1996). In our protocol of data acquisition and analysis, symmetric rectangular regions of interest (ROI) are also used for the quantitative measures positioning at several sites including the anterior and posterior pons, right and left midbrain, the right and left WM of temporal lobe, occipital lobe, posterior limb of the internal capsule, external capsule, anterior and posterior semiovale centrum (Tollard et al., 2009).

DWI and DTI show anomalies invisible on current morphological MRI even on T2* sequence (Huisman et al., 2003) and can better assess the degree of neurological impairment than any other conventional MRI sequence (Shanmuganathan et al., 2004). DTI permits to identify specific fiber bundles such as the corpus callosum and the long association fibers that include cingulum, superior and inferior longitudinal fascicules, uncinate fasciculus, superior and inferior fronto-occipital fascicules. Other fibers bundles can also be visualized: brainstem tracts, projection fibers such as corticospinal and corticothalamic fibers. DTI is an appropriate technique to assess microstructural WM damage that occurs in TBI, particularly since the pathophysiological mechanisms altering water diffusion anisotropy include DAI and intracranial hypertension. Several studies confirmed that DWI is a valuable technique to assess DAI (Arfanakis et al., 2002; Huisman et al., 2003; Liu et al., 1999) and showed that DTI is sensitive to damage in tissue that may appear normal on conventional MRI sequences (Arfanakis et al., 2002; Chan et al., 2003). Over conventional sequences commonly used to assess DAI (such as FLAIR, T2*, diffusion-weighted, and susceptibility weighted), DTI offers the advantages of a greater sensitivity and the availability of quantitative information.

Magnetic resonance spectroscopy protocol

MRS provides in vivo biochemical information. The metabolites that can be identified with proton MRS are dependent on the echo time (TE). At 1.5 T and 3 T, metabolites visualized utilizing intermediate-to-long TE (135–288 ms) include choline (Cho), creatine (Cr), N-acetylaspartate (NAA), and lactate (La). NAA is produced in the mitochondria of the neurons and transported into the neuronal cytoplasm and the axons. It is found in both gray and white matter in approximately equal quantities (Danielsen and Ross, 1999). In healthy subjects, there is an increase in NAA in gray matter from ventral to dorsal, and from the cerebral hemispheres to the spinal cord (Pouwels and Frahm, 1998). Several studies suggest NAA to be a brain osmolyte with possible reversible changes (Baslow et al., 2003, 2007; Moffett et al., 2007). It is considered as a marker of neuronal density and viability and functional status (Ebisu et al., 1994; Sullivan et al., 2001); its peak decrease when there is neuron suffering or loss. Choline is a metabolic marker of membrane synthesis and catabolism. MRS permits to detect free choline and phosphocholine, that is, those that are not incorporated into the macromolecules on the membrane surface (Ross and Michaelis, 1994). Its concentration is slightly greater in white than in gray matter. Its peak increases when there is greater membrane turnover, cell proliferation, or inflammatory process. Creatine is considered as a marker of the aerobic energy metabolism. It is assumed to be stable, hence is used for calculating metabolite ratios (NAA/Cr and Cho/Cr ratios). Lactate is at the limit of detectability in normal human brain using the routine spectroscopic techniques. However, under anaerobic glycolysis conditions, such as brain hypoxia, ischemia, or severe post-traumatic injury, lactate level may increase significantly.

In our view, a comprehensive MRS protocol to assess brain function in comatose patients should include single-voxel ^{1}H spectroscopy (SVS) placed on the posterior two-thirds of the pons (the parameters we typically use are: TR/TE, 1500/135 ms; matrix, 1 × 1; voxel thickness, 20 mm; and 96 averages) (Fig. 3) and an axial chemical shift imaging (CSI) at the level of the basal ganglia to include thalamus, insular cortex, and periventricular WM in the field of exploration (the parameters we typically use are: TR/TE, 1500/135 ms; field of view, 24 × 24 cm; matrix, 18 × 18; slice thickness, 15 mm; and NEX, 1) (Tollard et al., 2009) (Fig. 4). In our clinical practice, the SVS is usually performed in the pons for three reasons. First, the pons contains a large part of the ascending reticular activating system; second, the pons is often affected by DAIs not necessarily seen on FLAIR and T2* sequences; and third, the pons can be damaged from both primary and secondary cerebral injuries due to temporal lobe herniation (Carpentier et al., 2006). Patients with bilateral lesions of the protuberance on standard morphological MRI sequences have been reported with a 100% mortality rate (Firsching et al., 1998). Finally, MRS has a better sensitivity than T2*sequence in the detection of ischemic or hemorrhagic diffuse axonal lesions in TBI (Cecil et al., 1998).

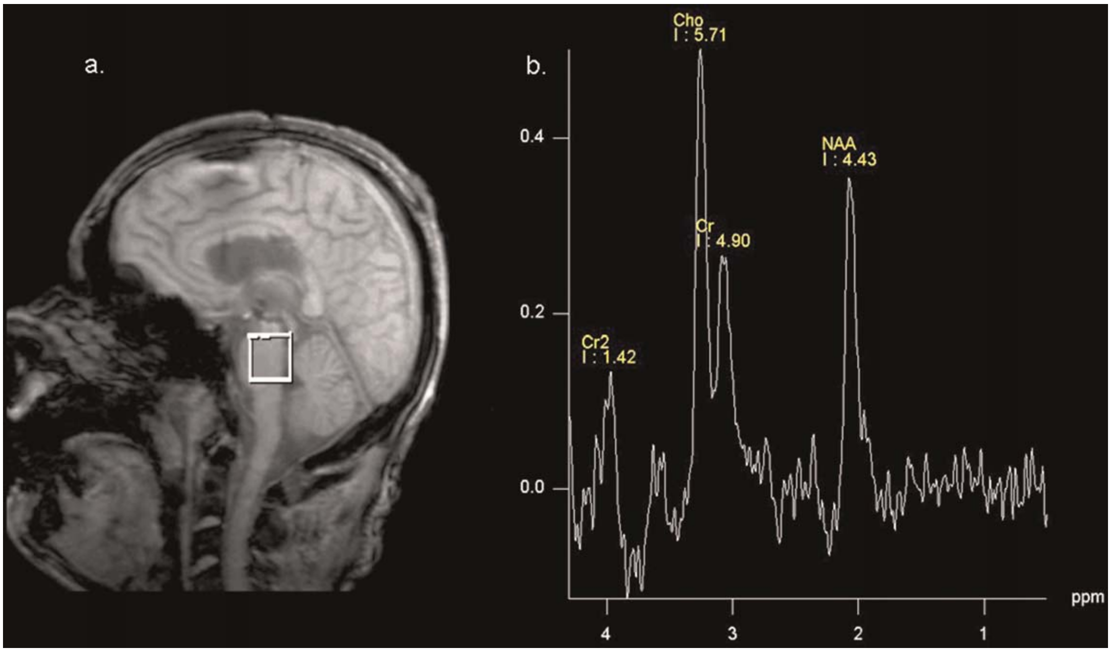


Fig. 3. Monovoxel spectroscopic (SVS) of the pons in a TBI patient. a: Location of the voxel on the sagittal T1-weighted acquisition. b: Decreased NAA spectrum (NAA/Cr = ~~0.~~90 and NAA/Cho+Cr+NAA = ~~0.~~29).

Comatose patients assessment

The timing of an optimal MRI assessment in comatose patients remains controversial (Table 1). An acute exploration may take into account reversible lesions such as edema or miss secondary lesions due to intracranial hypertension or systemic disorders. On the contrary, an examination performed late after the injury may only detect sequels such as global aspecific atrophy and has no impact on the initial medical management and on altered state of consciousness status prediction. With regard to time since TBI or stroke, MRS and DTI findings vary greatly and studies are heterogeneous as illustrated by last studies performed with MRS sequences. Four phases may be distinguished: an acute phase, which lasts 24 h after TBI; an early subacute phase, from the day 1 to 13; a late subacute phase, from days 14 to 20; and a chronic phase, which starts on day 21 (Weiss et al., 2007). Among these MRS studies, two included patients at the acute phase (Marino et al., 2007; Ross et al., 1998), two from the early subacute phase to the first month (Carpentier et al., 2006; Garnett et al., 2000), one at the late subacute phase up to 11 months (Choe et al., 1995), and four at the chronic phase from 3 weeks to 8 months after TBI (Friedman et al., 1999; Ricci et al., 1997; Sinson et al., 2001; Uzan et al., 2003). In a retrospective study using DTI, comatose patients were excluded if the time delay between trauma and MRI exceeded 7 days to avoid the various changes in anisotropic diffusion related to secondary tissue injury (Huisman et al., 2004). An early examination with precise quantification of the extent and degree of brain injury is essential for treatment decisions (i.e., to determine outcome, cognitive and behavioral deficits), and becomes a criterion of good practice in management of these patients. The late subacute phase seems to be the best moment to assess comatose patients taking into account the physiopathology and all issues (medical, ethical, legal, social) raised by the management of these patients.

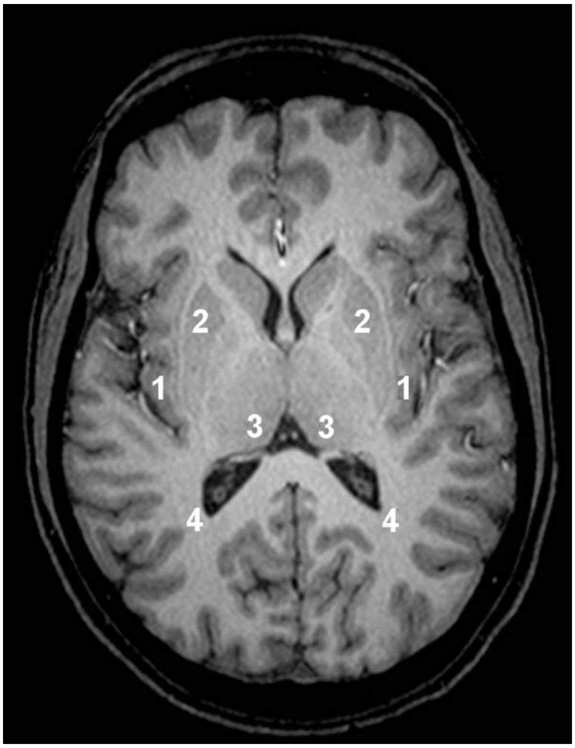


Fig. 4. Chemical shift imaging (CSI). Position of regions of interest: insula (1), lenticular nucleus (2), thalamus (3), and periventricular white matter (4).

Prediction of outcome with MRI

Although clinical examination and conventional imaging techniques provide useful information for TBI patient screening and acute care, none of them accurately predicts individual patient outcome. Developing a reliable MRI outcome-prediction tool is a major challenge for all physicians in charge of comatose patients. It would provide an objective basis for deciding to go on with prolonged aggressive care or to remove life-supporting therapy as well as for informing families and planning rehabilitation.

Conventional MRI

There is some evidence that MRI may have potential in terms of predicting outcome according to several studies performed with conventional MRI. Firsching and colleagues (1998) performed a prospective MRI study in 61 consecutive patients within 7 days after their injury. They found bilateral pontine lesions to be 100% fatal, whereas unilateral brainstem lesions were responsible of similar mortality rate as in patients with no brainstem injury and conclude that early MRI after head injury had a higher predictive value than CT scanning. Other studies have showed that MRI scans performed at acute and subacute phase after head injury provide several indicators for unfavorable outcome when there are lesions within the corpus callosum and dorsolateral brainstem (Kampfl et al.,1998), basal ganglia, hippocampus, midbrain, and pons (Wedekind et al., 1999). Presence of hemorrhage in DAI-type lesions and the association with traumatic space-occupying lesions was indicative of poor prognostic sign. Isolated non-hemorrhagic DAI-type lesions were not associated with poor clinical outcome (Paterakis et al., 2000). Hoelper et al. (2000) observed that the number (>3) and volume (>1.5 mL) of brainstem lesions correlated with unfavorable outcome. There are also some evidences that the total lesion volume on FLAIR images correlates significantly with clinical outcome. The volume of lesions of the corpus callosum on the FLAIR sequence correlated significantly with scores on disability and cognition scales at the first clinical assessment. Volume of FLAIR lesions in the frontal lobes correlated significantly with outcome after 1 year (Pierallini et al., 2000). Moreover, the number of lesions detected by T2* was also shown as significantly greater than that detected by T2-FSE (Yanagawa et al., 2000). Lesions detected by T2* and FLAIR were inversely correlated with outcome of patient (Yanagawa et al., 2000; Carpentier et al., 2006).

In spite of these multiple morphological MRI studies and their encouraging results (Table 1), it remains difficult to explain why some patients in persistent vegetative state or with long-term marked cognitive impairments have no or minimal lesions on conventional MR examination performed with T2* and diffusion sequences. Therefore, morphological MRI alone cannot be considered as a reliable tool to assess coma severity, and to predict the comatose patient functional outcome.

Magnetic resonance spectroscopy

To our knowledge, Choe et al. (1995) performed the first assessment of patient with closed head injury using in vivo proton MRS to evaluate neuronal and axonal dysfunction. The main result in this case-control study was a significant decrease of NAA/Cr ratio compared with normal controls. The level of NAA/Cr ratio was significantly correlated with Glasgow Outcome Scale (GOS; Jennett and Bond, 1975) whereas no clear correlation of other metabolite ratios such as Cho/Cr was observed. Since then, several investigations that do appear in the literature were promising in terms of the role of proton MRS as an accurate tool to predict patient outcome. Ricci et al. (1997) examined 14 vegetative brain-injured patients with proton magnetic resonance single-volume spectroscopy performed 1–90 months after the injury. Cho/Cr was significantly higher, whereas NAA/Cho and NAA/Cr were markedly lower than in the control subjects. The NAA/Cho ratio was statistically significant in discriminating between the patients with a poor outcome (GOS score, 1–2) and those who regained awareness. Other studies have showed a reduced NAA/Cr level in gray and white matter of occipito-parietal regions in acute and subacute phase after injury, which correlated with bad outcome (Ross et al., 1998; Friedman et al., 1999). The frontal WM NAA/Cr acquired in the subacute phase significantly correlated with patient outcome, whereas Cho/Cr was increased at both the early and late phase compared with controls (Garnett et al., 2000). Decreased NAA/Cr ratio in the splenium of corpus callosum also correlated with the GOS score of acute and chronic patients (Sinson et al., 2001). The NAA/Cr ratio was reduced in the thalami of both persistent vegetative patients and patients who recovered 6–8 months after injury (Uzan et al., 2003). Moreover, NAA/Cr ratios were lower in persistent vegetative patient than in patients who regained awareness. Carpentier et al. (2006) observed three MRS profile of the pons after TBI: normal profile (the peak of NAA is higher than the peaks of Cho and Cr), neuronal loss profile (the NAA peak is decreased, nearly to the level of the Cr peak; the NAA/Cr ratio is <1.50 and NAA/Cho+Cr+NAA<0.40) (Fig. 3), and gliosis profile (increased Cho peak with no change in the Cr or NAA peak and Cho/Cr>NAA/Cr or Cho/Cho+Cr+NAA>0.40).

The NAA/Cr ratio was correlated with the GOS score but not with lesions burden on T2* or FLAIR, whereas this lesions burden was correlated with the outcome score. Therefore, MRS and conventional MR seem to be complementary. The combination of these two techniques may be useful. Other people showed that NAA/Cr and NAA/all metabolites ratios to be significantly lower in the medial cortex of patients with TBI than in normal controls, whereas the La/Cr and La/all metabolites ratios were increased (Marino et al., 2007). Both NAA and La ratios correlated with GOS score. Data of MRS performed early after brain injury are clinically relevant. Increased La detected may be, at this stage, a reliable index of injury severity and disease outcome in patients with TBI. Cohen et al. (2007) included 20 patients in a case-control study with the purpose to quantify the global decline of the neuronal marker NAA, as well as gray and white matter atrophy after mild traumatic brain injury (mTBI). Patients with mTBI exhibited, on average, a 12% whole-brain NAA deficit, which increased with age, as compared with the control subjects. Volumetric MRI in their patients showed decreased volume of gray matter, which, in combination with low whole-brain NAA, strongly suggests damage to the neurons and their axons. Tollard et al. (2009) observed NAA/Cr values at all measurement sites to be lowest in group of patients with unfavorable outcome (GOS, 1–3), intermediate in patients with favorable outcome (GOS, 4–5), and highest in control group. They did not find correlations between metabolic ratios and FA values; in particular, the NAA/Cr ratio of the pons was not correlated with the infratentorial FA value. Interestingly an unfavorable outcome after 1 year was predicted with up to 86% sensitivity and 97% specificity when taking into account both DTI and MRS values. Sensitivity was 79% and specificity 85% with FA only; corresponding values with MRS only were 75% and 75%.

In conclusion, proton MRS should be added to morphological MR examinations with minimal additional time. It is proved to be useful in assessing injury severity, guiding patient care, and predicting patient outcome (Table 1). We agree with Weiss et al. (2007) that MRS studies in TBI patients are heterogeneous in terms of patient selection, time from TBI to MRS, voxel location, method of outcome assessment, and timing of outcome assessment. MRS research suffers from disparate acquisition protocols across research teams. However, the normal NAA/Cr ratio in identical regions is similar across studies and its decrease appears to be a reliable index of unfavorable outcome. The NAA is shown to decrease within a few minutes after TBI and reach the trough value within 48 h. Its level remains stable within the first month after TBI, supporting the validity of MRS assessment during the second or third week (Holshouser et al., 2006; Signoretti et al., 2002). The later evolution of the NAA/Cr ratio between 6 weeks and 1 year after TBI is more heterogeneous, and NAA levels have been shown to decrease or increase. This possible variability in NAA levels is a potential limitation of this technique. In addition, the use of ratios may be problematic in TBI. Cr is assumed to be stable in normal brain tissue and used to standardize other brain metabolites. However, to the best of our knowledge, there is no evidence that Cr is invariable in TBI. Indeed, it could be affected similarly to the metabolite of interest as well (it is suggested to be reduced in hypermetabolic and raised in hypometabolic states; Castillo et al., 1996; Wood et al., 2003). This issue is important in particular as metabolism may be compromised in mTBI (Lewine et al., 1999). To minimize the potential negative impact of the NAA variability, repeated MRS examination during the subacute phase is probably needed and the whole-brain NAA estimation would improve the MRS yield. Studies have to be performed to prove the stability of Cr in TBI.

Diffusion tensor imaging

DTI may be a valuable biomarker for the severity of tissue injury and a predictor for outcome. It reveals changes in the WM that are correlated with both acute GCS and Rankin scores at discharge (Huisman et al., 2004). Significant early reduction of anisotropy was observed in WM structures, in particular in the internal capsule and the corpus callosum, which are the sites most commonly involved by DAI (Arfanakis et al., 2002). Moreover, several regions recovered normal values of anisotropy 1 month after the injury (Arfanakis et al., 2002). Xu et al. (2007) found significant differences in the corpus callosum, internal and external capsule, superior and inferior longitudinal fascicles, and the fornix in TBI patients. They showed that FA and ADC measurements offered superior sensitivity compared to conventional MRI diagnosis of DAI. Salmond et al. (2006) reported increased diffusivity in TBI patients at least 6 months after their injury in the cerebellum, frontal, insula, cingulate, parietal, temporal, and occipital lobes.

The anisotropy seems to be reduced both in the major WM tracts such as the corpus callosum and the internal and external capsule, and the associative fibers underlying the cortex. DTI has a number of advantages as an imaging biomarker of brain injury: first, it can be used to evaluate brain trauma in an unconscious or sedated patient; second, it could permit the evaluation of responses to treatment even when the clinical scores are inadequate for assessing the patient; third, quantitative DTI measurements are unlikely to be tainted by adverse central nervous system (CNS) effects of hypnotic drugs, unlike clinical scores; and fourth, DTI may be an important alternative marker, as low initial GCS scores are of limited value in predicting the prognosis (Huisman et al., 2004). Finally, Perlbarg et al. (2009) showed significant FA differences between favorable and unfavorable 1-year outcome groups around four FA tracks: in inferior longitudinal fasciculus, posterior limb of the internal capsule, cerebral peduncle, and posterior corpus callosum.

Conclusion

In the future, DTI and MRS may permit to evaluate response to therapeutic interventions in TBI even when the clinical scores are inadequate for assessing the patient. MRS and DTI detect abnormalities not demonstrated on conventional MRI or CT structural scans, which are generally correlated with clinical outcomes. It is becoming increasingly obvious that these techniques are complementary and that both could be required to explore comatose patients at subacute stage from TBI as part of a comprehensive multimodal MRI and clinical assessment. Their combination will also possibly allow the pathogenesis of brain impairment to be better understood and the outcome better predicted. However, it is important to keep in mind some pitfalls such as the variability of NAA values and the impact of brain swelling which can, respectively, diminish the reliability of NAA and early FA measurement for predicting outcome in individual brain-damaged patients.

Acknowledgments

This research was supported by the Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge & COST BM0605), McDonnell Foundation, Mind Science Foundation, Reine Elisabeth Medical Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340) and University and University Hospital of Liège. A. Vanhaudenhuyse was funded by ARC 06/11-340; M. Boly, and S. Laureys are, respectively, Research Fellow, Postdoctoral Researcher, and Senior Research Associate at FRS. The authors thank the technicians of the Department of Neuro-Radiology and the nurses of the Intensive Care Units of the Pitié-Salpêtrière Hospital, Paris and Centre Hospitalier Universitaire, Liège, for their active participation in the MRI studies in comatose patients.

References

Adams, J. H., Graham, D. I., Murray, L. S., & Scott, G. (1982). Diffuse axonal injury due to nonmissile head injury in humans: An analysis of 45 cases. *Annals of Neurology*, *12*, 557–563.

Anderson, C. V., Wood, D. M., Bigler, E. D., & Blatter, D. D. (1996). Lesion volume, injury severity, and thalamic integrity following head injury. *Journal of Neurotrauma*, *13*, 59–65.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*(7048), 13–16.

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *American Journal of Neuroradiology*, *23*, 794–802.

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *Journal of Molecule Neuroscience*, *34*, 51–61.

Baslow, M. H., Hrabe, J., & Guilfoyle, D. N. (2007). Dynamic relationship between neurostimulation and N-acetylaspartate metabolism in the human visual cortex: Evidence that NAA functions as a molecular water pump during visual stimulation. *Journal of Molecule Neuroscience*, *32*, 235–245.

Baslow, M. H., Suckow, R. F., Gaynor, K., Bhakoo, K. K., Marks, N., Saito, M., et al. (2003). Brain damage results in down-regulation of N-acetylaspartate as a neuronal osmolyte. *Neuromolecular Medicine*, *3*, 95–104.

Beuthien-Baumann, B., Handrick, W., Schmidt, T., Burchert, W., Oehme, L., Kropp, J., et al. (2003). Persistent vegetative state: Evaluation of brain metabolism and brain perfusion with PET and SPECT. *Nuclear Medicine Communications*, *24*, 643–649.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008a). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology*, *7*(11), 1013–1020.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., et al. (2008b). Intrinsic brain activity in altered states of consciousness. How conscious is the default mode of brain function? *Annals of the New York Academy of Sciences*, *1129*, 119–129.

Carpentier, A., Galanaud, D., Puybasset, L., Muller, J. C., Lescot, T., Boch, A. L., et al. (2006). Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect ‘‘invisible brain stem damage’’ and predict ‘‘vegetative states’’. *Journal of Neurotrauma*, *23*, 674–685.

Castillo, M., Kwock, L., & Mukherji, S. K. (1996). Clinical applications of proton MR spectroscopy. *American Journal of Neuroradiology*, *17*, 1–15.

Cecil, K. M., Hills, E. C., Sandel, M. E., Smith, D. H., McIntosh, T. K., Mannon, L. J., et al. (1998). Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. *Journal of Neurosurgery*, *88*, 795–801.

Celesia, G. (1993). Persistent vegetative state. *Neurology*, *43*, 1457–1458.

Chan, Y. L., Chu, W. C., Wong, G. W., & Yeung, D. K. (2003). Diffusion-weighted MRI in shaken baby syndrome. *Pediatric Radiology*, *33*, 574–577.

Childs, N. L., & Mercer, W. N. (1996). Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs. *British Medical Journal*, *313*(7062), 944.

Choe, B. Y., Suh, T. S., Choi, K. H., Shinn, K. S., Park, C. K., & Kang, J. K. (1995). Neuronal dysfunction in patients with closed head injury evaluated by in vivo 1H magnetic resonance spectroscopy. *Investigative Radiology*, *30*, 502–506.

Cohen, B. A., Inglese, M., Rusinek, H., Babb, J. S., Grossman, R. I., & Gonen, O. (2007). Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. *American Journal of Neuroradiology*, *28*, 907–913.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*, 2494–2507.

Cox, I. J. (1996). Development and applications of in vivo clinical magnetic resonance spectroscopy. *Progress in Biophysics and Molecular Biology*, *65*, 45–81.

Danielsen, E. R., & Ross, B. (1999). *Magnetic resonance spectroscopy diagnosis of neurological diseases* (1st ed.). New York: Marcel Dekker, Inc.

Ebisu, T., Rooney, W. D., Graham, S. H., Weiner, M. W., & Maudsley, A. A. (1994). N-acetylaspartate as an in vivo marker of neuronal viability in kainate-induced status epilepticus: 1H magnetic resonance spectroscopic imaging. *Journal of Cerebral Blood Flow & Metabolism*, *14*, 373–382.

Firsching, R., Woischneck, D., Diedrich, M., Klein, S., Ruckert, A., Wittig, H., et al. (1998). Early magnetic resonance imaging of brainstem lesions after severe head injury. *Journal of Neurosurgery*, *89*, 707–712.

Friedman, S., Brooks, W., Jung, R., Chiulli, S., Sloan, J., Montoya, B., et al. (1999). Quantitative proton MRS predicts outcome after traumatic brain injury. *Neurology*, *52*, 1384–1391.

Gale, S. D., Johnson, S. C., Bigler, E. D., & Blatter, D. D. (1995). Trauma-induced degenerative changes in brain injury: A morphometric analysis of three patients with preinjury and postinjury MR scans. *Journal of Neurotrauma*, *12*, 151–158.

Garnett, M. R., Blamire, A. M., Corkill, R. G., Cadoux-Hudson, T. A., Rajagopalan, B., & Styles, P. (2000). Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain*, *123*, 2046–2054.

Gean, A. D. (1994). *White matter shearing injury and brainstem injury*. New York: Raven.

Gentry, L. R., Godersky, J. C., Thompson, B., & Dunn, V. D. (1988). Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. *American Journal of Roentgenology*, *150*, 673–682.

Gerber, D. J., Weintraub, A. H., Cusick, C. P., Ricci, P., & Whiteneck, G. G. (2004). Magnetic resonance imaging of traumatic brain injury: Relationship of T2*SE and T2GE to clinical severity and outcome. *Brain Injury*, *18*, 1083–1097.

Hoelper, B. M., Soldner, F., Chone, L., & Wallenfang, T. (2000). Effect of intracerebral lesions detected in early MRI on outcome after acute brain injury. *Acta Neurochirurgica. Supplement*, *76*, 265–267.

Holshouser, B. A., Tong, K. A., Ashwal, S., Oyoyo, U., Ghamsary, M., Saunders, D., et al. (2006). Prospective longitudinal proton magnetic resonance spectroscopic imaging in adult traumatic brain injury. *Journal of Magnetic Resonance Imaging*, *24*, 33–40.

Huisman, T., Sorensen, A., Hergan, K., Gonzalez, R., & Schaefer, P. (2003). Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *Journal of Computer Assisted Tomography*, *27*, 5–11.

Huisman, T. A., Schwamm, L. H., Schaefer, P. W., Koroshetz, W. J., Shetty-Alva, N., Ozsunar, Y., et al. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *American Journal of Neuroradiology*, *25*, 370–376.

Jennett, B. (2005). 30 years of the vegetative state: Clinical, ethical and legal problems. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology* (Vol. 150, pp. 541–548). Amsterdam: Elsevier.

Jennett, B., & Bond, M. (1975). Assessment of outcome after severe brain damage. *Lancet*, *7905*, 480–484.

Kampfl, A., Schmutzhard, E., Franz, G., Pfausler, B., Haring, H. P., Ulmer, H., et al. (1998). Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet*, *351*, 1763–1767.

Katz, D. (1997). *Traumatic brain injury*. Malden: Blackwell Science.

Kelly, A. B., Zimmerman, R. D., Snow, R. B., Gandy, S. E., Heier, L. A., & Deck, M. D. F. (1988). Head trauma: Comparison of MR and CT-experience in 100 patients. *American Journal of Neuroradiology*, *9*, 699–708.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (1999). Impaired effective cortical connectivity in vegetative state. *Neuroimage*, *9*, 377–382.

Lewine, J. D., Davis, J. T., Sloan, J. H., Kodituwakku, P. W., & Orrison, W. W., Jr. (1999). Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma. *American Journal of Neuroradiology*, *20*, 857–866.

Liu, A. Y., Maldjian, J. A., Bagley, L. J., Sinson, G. P., & Grossman, R. I. (1999). Traumatic brain injury: Diffusion-weighted MR imaging findings. *American Journal of Neuroradiology*, *20*, 1636–1641.

Marino, S., Zei, E., Battaglini, M., Vittori, C., Buscalferri, A., Bramanti, P., et al. (2007). Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. *Jounral of Neurology, Neurosurgery and Psychiatry*, *78*, 501–507.

Melhem, E. R., Itoh, R., Jones, L., & Barker, P. B. (2000). Diffusion tensor MR imaging of the brain: Effect of diffusion weighting on trace and anisotropy measurements. *American Journal of Neuroradiology*, *21*, 1813–1820.

Moffett, J. R., Ross, B., Arun, P., Madhavarao, C. N., & Namboodiri, A. M. (2007). N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Progress in Neurobiology*, *81*, 89–131.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). Neuroimaging and the vegetative state: Resolving the behavioral assessment dilemma? *Annals of the New York Academy of Sciences*, *1157*(March), 81–89.

Murray, J. G., Gean, A. D., & Evans, S. J. (1996). Imaging of acute head injury. *Seminars in Ultrasound, CT and MRI*, *17*, 185–205.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *13*, 1402.

Parvizi, J., & Damasio, A. (2001). Consciousness and the brainstem. *Cognition*, *79*, 135–160.

Paterakis, K., Karantanas, A. H., Komnos, A., & Volikas, Z. (2000). Outcome of patients with diffuse axonal injury: The significance and prognostic value of MRI in the acute phase. *Journal of Trauma*, *49*, 1071–1075.

Payne, K., Taylor, R. M., Stocking, C., & Sachs, G. A. (1996). Physicians' attitudes about the care of patients in the persistent vegetative state: A national survey. *Annals of Internal Medicine*, *125*, 104–110.

Perlbarg, V., Puybasset, L., Tollard, E., Lehéricy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. *Human Brain Mapping* (in press).

Pierallini, A., Pantano, P., Fantozzi, L. M., Bonamini, M., Vichi, R., Zylberman, R., et al. (2000). Correlation between MRI findings and long-term outcome in patients with severe brain trauma. *Neuroradiology*, *42*, 860–867.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*, 637–648.

Plum, F., & Posner, J. (1980). *The diagnosis of stupor and coma* (3rd ed.). Oxford, UK: Oxford University Press.

Pouwels, P. J., & Frahm, J. (1998). Regional metabolite concentrations in human brain as determined by quantitative localized proton MRS. *Magnetic Resonance Medicine*, *39*, 53–60.

Ricci, R., Barbarella, G., Musi, P., Boldrini, P., Trevisan, C., & Basaglia, N. (1997). Localised proton MR spectroscopy of brain metabolism changes in vegetative patients. *Neuro radiology*, 313–319.

Ross, B., & Michaelis, T. (1994). Clinical applications of magnetic resonance spectroscopy. *Magnetic Resonance Quarterly*, *10*, 191–247.

Ross, B. D., Ernst, T., Kreis, R., Haseler, L. J., Bayer, S., Danielsen, E., et al. (1998). 1H MRS in acute traumatic brain injury. *Journal of Magnetic Resonance Imaging*, *8*, 829–840.

Salmond, C. H., Menon, D. K., Chatfield, D. A., Williams, G. B., Pena, A., Sahakian, B. J., et al. (2006). Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *Neuroimage*, *29*, 117–124.

Schaefer, P. W., Huisman, T. A. G., Sorensen, A. G., Gonzalez, R. G., & Schwamm, L. H. (2004). Diffusion-weighted MR imaging in closed head injury: High correlation with initial Glasgow Coma Scale score and score on Modified Ranking Scale at Discharge. *Radiology*, *233*(1), 58–66.

Scheid, R., Preul, C., Gruber, O., Wiggins, C., & von Cramon, D. Y. (2003). Diffuse axonal injury associated with chronic traumatic brain injury: Evidence from T2*-weighted gradient-echo imaging at 3 T. *American Journal of Neuroradiology*, *24*, 1049–1056.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *21*(9), 35.

Selden, N., Gitelman, D., Salamon-Murayama, N., Parrish, T., & Mesulam, M. (1998). Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain*, *121*, 2249–2257.

Shanmuganathan, K., Gullapalli, R. P., Mirvis, S. E., Roys, S., & Murthy, P. (2004). Whole-brain apparent diffusion coefficient in traumatic brain injury: Correlation with Glasgow Coma Scale. *American Jounral of Neuroradiogy*, *25*, 539–544.

Signoretti, S., Marmarou, A., Fatouros, P., Hoyle, R., Beaumont, A., Sawauchi, S., et al. (2002). Application of chemical shift imaging for measurement of NAA in head injured patients. *Acta Neurochirurgica. Supplement*, *81*, 373–375.

Sinson, G., Bagley, L. J., Cecil, K. M., Torchia, M., McGowan, J. C., Lenkinski, R. E., et al. (2001). Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: Correlation with clinical outcome after traumatic brain injury. *American Journal Neuroradiology*, *22*, 143–151.

Strich, S. J. (1961). Shearing of nerve fibres as a cause of brain damage due to head injury: A pathological study of twenty cases. *Lancet*, *2*, 443–448.

Sullivan, E. V., Adalsteinsson, E., Spielman, D. M., Hurd, R. E., & Pfefferbaum, A. (2001). N-acetylaspartate — A marker of neuronal integrity. *Annals of Neurology*, *50*, 824–825.

Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., et al. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine*, *37*, 1448–1455.

Trivedi, M. A., Ward, M. A., Hess, T. M., Gale, S. D., Dempsey, R. J., Rowley, H. A., et al. (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: Relationship with duration of coma. *Journal of Neurotrauma*, *24*(5), 766–771.

Uzan, M., Albayram, S., Dashti, S. G., Aydin, S., Hanci, M., & Kuday, C. (2003). Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. *Journal of Neurolology, Neurosurgery and Psychiatry*, *74*, 33–38.

Voss, H. U., Uluç, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *The Journal of Clinical Investigation*, *116*(7), 1823–1825.

Wedekind, C., Fischbach, R., Pakos, P., Terhaag, D., & Klug, N. (1999). Comparative use of magnetic resonance imaging and electrophysiologic investigation for the prognosis of head injury. *Journal of Trauma*, *47*, 44–49.

Weiss, N., Galanaud, D., Carpentier, A., Naccache, L., & Puybasset, L. (2007). Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. *Critical Care*, *11*, 230.

Wood, S. J., Berger, G., Velakoulis, D., Phillips, L. J., McGorry, P. D., Yung, A. R., et al. (2003). Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. *Schizophrenia Bulletin*, *29*, 831–843.

Xu, J., Rasmussen, I. A., Lagopoulos, J., & Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *Journal of Neurotrauma*, *24*, 753–765.

Yanagawa, Y., Tsushima, Y., Tokumaru, A., Un-no, Y., Sakamoto, T., Okada, Y., et al. (2000). A quantitative analysis of head injury using T2*-weighted gradient-echo imaging. *Journal of Trauma*, *49*, 272–277.