Exploration of residual language abilities in patients with disorders of consciousness

Charlène Aubinet

Promotor: Prof. Steven Laureys

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Supervisor

Prof. Steven Laureys, MD, PhD, Université de Liège

Assessment committee

Prof. Didier Ledoux (president), MD, PhD, Université de Liège

Prof. Philippe Peigneux, PhD, Université Libre de Bruxelles

Dr Caroline Schnakers, PhD, University of California, Los Angeles

Prof. Steve Majerus, PhD, Université de Liège

Dr Martine Poncelet, PhD, Université de Liège

Dr Mohamed Ali Bahri, PhD, Université de Liège

Dr Olivia Gosseries, PhD, Université de Liège

Dr Charlotte Martial (secretary), PhD, Université de Liège

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To all (minimally) conscious patients
who can understand us
but cannot communicate it...

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Scientific publications

The present thesis is based on the following publications:

Articles:

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Aubinet C, Cassol H, Gosseries O, Bahri MA, Larroque SK, Majerus S, Martial C, Martens G, Carrière M, Chatelle C, Laureys S, & Thibaut A (2020). Brain metabolism but not grey matter volume underlies the presence of language function in the minimally conscious state. *Neurorehabilitation and Neural Repair, 34*(2), 172-184.

Aubinet C, Larroque S, Heine L, Martial C, Majerus S, Laureys S, Di Perri C (2018). Clinical subcategorization of minimally conscious state according to resting functional connectivity. *Human Brain Mapping, 39*(11), 4519-4532.

Aubinet C, Panda R, Larroque SK, Cassol H, Bahri MA, Carrière M, Wannez S, Majerus S, Laureys S, Thibaut A (2019). Reappearance of command-following is associated with the recovery of language and internal-awareness networks: A longitudinal multiple-case report. *Frontiers in Systems Neuroscience, 13*(8), 1-6.

Aubinet C, Murphy L, Bahri MA, Larroque SK, Cassol H, Annen J, Carrière M, Wannez S, Thibaut A, Laureys S, Gosseries O (2018). Brain, behavior and cognitive interplay in disorders of consciousness: A multiple case study. *Frontiers in Neurology, 9*(665).

Aubinet C, Chatelle C, Gillet S, Lejeune N, Cassol H, Thunus M, Hennen N, Laureys S, & Majerus S (*in preparation*). The Brief Evaluation of Receptive Aphasia test for the detection of language impairment in severely brain-injured patients.

Glossary

AC Aphasic Conscious

BERA Brief Evaluation of Receptive Aphasia

BOLD Blood-Oxygen-Level-Dependent

CAVE Cognitive Assessment by Visual Election

CRS-R Coma Recovery Scale-Revised

DLPFC Dorso-Lateral PreFrontal Cortex

DMN Default Mode Network

DoC Disorders of Consciousness

DTI Diffusion Tensor Imaging

EEG Electroencephalography

FDG-PET Fluorodeoxyglucose Positron Emission Tomography

fMRI Functional magnetic Resonance Imaging

FPN Frontoparietal Network

FWHM Full-Width at Half-Maximum

HCS Healthy Control Subjects

IPL Inferior Parietal Lobule

LIS Locked-In Syndrome

MCS Minimally Conscious State

MCS- Minimally Conscious State Minus

MCS+ Minimally Conscious State Plus

MPFC	Medial PreFrontal Cortex
MRI	Magnetic Resonance Imaging
NTBI	Non-Traumatic Brain Injury
PCC	Posterior Cingulate Cortex
ROI	Region Of Interest
SON	Subject's Own Name
STG	Superior Temporal Gyrus
TBI	Traumatic Brain Injury
UWS	Unresponsive Wakefulness Syndrome
VBM	Voxel-Based Morphometry

Summary

Language assessment in post-comatose patients with disorders of consciousness is complicated by their limited behavioral repertoire. In addition, language deficits might prevent consistent responses to verbal instructions, leading to an underestimation of consciousness in aphasic patients. The introduction therefore includes a systematic review of the literature investigating the residual language abilities in patients with disorders of consciousness after severe brain injury, based on data extracted for four main outcomes: (1) bedside language behavioral assessments, (2) language-related signs of consciousness, (3) detection of covert command-following and communication using brain-computer interfaces, and (4) cortical activity related to speech processing. This review stresses the need for new valid bedside language behavioral assessments.

The **Experimental part I** aims to investigate, in three retrospective studies, the neural correlates of command-following, intelligible verbalization and/or intentional communication. These language-related signs of consciousness, which are observed in the minimally conscious state *plus* but not in the minimally conscious state *minus*, are detected by the Coma Recovery Scale-Revised (CRS-R). **Study 1** investigates brain glucose metabolism (by means of fluorodeoxyglucose-positron emission tomography; FDG-PET) and grey matter volume (by means of voxel-based morphometry) in both minimally conscious state subcategories. Our findings suggest that brain function in the language network is determinant for recovery of language-related signs of consciousness. Indeed, the minimally conscious state *plus* group presented higher metabolism mainly in the left middle temporal cortex, known to be involved in semantic processing, compared to the minimally conscious state *minus* group. The left angular gyrus was also functionally disconnected from the left prefrontal cortex in minimally conscious state *minus* compared to minimally conscious state *plus* (i.e., frontoparietal network). Nevertheless, no significant differences were found in grey matter volume between patient groups. **Study 2** further explores the brain function underlying the aforementioned clinical sub-categorization, by focusing on resting state

functional connectivity (by means of magnetic resonance imaging) in minimally conscious state *minus* and *plus* groups. Higher connectivity was found in minimally conscious state *plus* compared to minimally conscious state *minus* in the left frontoparietal network (i.e., executive language control network), specifically between the left dorso-lateral prefrontal cortex and left temporo-occipital fusiform cortex, which is involved in semantic processing. Minimally conscious state *plus* and *minus* groups would however not be differentiated by networks associated with auditory processing, perception of surroundings and internal awareness, nor by inter-hemispheric integration and structural brain damage. Indeed, no differences were observed between both subcategories in the auditory network, right frontoparietal network, default mode network, thalamocortical and interhemispheric connectivity, between-network anticorrelations and grey/white matter volume. **Study 3** finally reports longitudinal brain glucose metabolism and grey matter volume data of three patients who were firstly diagnosed as minimally conscious state *minus*, and then as minimally conscious state *plus,* after recovery of command-following. At this second time point, they showed less hypometabolism and/or higher grey matter volume in regions previously associated with self-consciousness such as the precuneus and thalamus, as well as in language-related regions such as the left caudate and temporal/angular cortices. Hence, both FDG-PET and voxel-based morphometry techniques enabled differentiating minimally conscious state *minus* and minimally conscious state *plus* at the single-subject level. Better characterizing the neural correlates of residual cognitive abilities of minimally conscious patients contributes to reducing the risk of misdiagnosis and adapting therapeutic approaches.

The **Experimental part II** rather focuses on bedside language assessment attempts in several patients with disorders of consciousness. New behavioral tools are being developed and used in comparison with CRS-R, FDG-PET and voxel-based morphometry assessments. **Study 4** presents the utility of the Cognitive Assessment by Visual Election (CAVE) in assessing recognition of objects, pictures, letters, numbers, written words and colors in five post-comatose patients in minimally conscious state or emerging from the minimally conscious state. The CAVE scores decreased along with

the CRS-R total score, establishing a consistent behavioral/cognitive profile for each patient. All patients also showed structural and functional brain impairments (using FDG-PET and voxel-based morphometry) corresponding to their behavioral/cognitive profile as based on previous literature. Brain-behavior relationships might therefore be hypothesized even in severely brain-injured patients. As the CAVE does not distinguish various language domains nor does it include items controlling for psycholinguistic effects, we finally created the Brief Evaluation of Receptive Aphasia (BERA). This tool assesses receptive phonology, semantics and morphosyntax based on visual selection of a target-picture next to a specific distractor. **Study 5** describes the administration of the BERA to 10 healthy subjects (to ensure they were able to perform perfectly), 52 aphasic conscious patients and 4 patients in minimally conscious state or emerging from the minimally conscious state. In aphasic conscious patients, the BERA showed satisfactory intra- and inter-rater reliability, internal and concurrent validity. In post-comatose patients, the BERA scores suggested the presence of specific receptive difficulties for phonological, semantic and particularly morphosyntax subscales. The results were in line with functional (FDG-PET) and structural (voxel-based morphometry) neuroimaging data. The BERA may complement the CRS-R to diagnose patients' disorders of consciousness and refine their cognitive and language profile.

To conclude, this thesis is based on multimodal assessments of patients in minimally conscious state or emerging from the minimally conscious state and provides new insights with regard to the characterization of their language residual abilities. Our studies also constitute a new step toward the disentanglement of consciousness and language impairments in these severely brain-injured patients. Future studies should optimize the CAVE and BERA assessments and repeat them on larger samples of post-comatose patients. Neural correlates of specific language impairments should also be investigated in these patients with severe brain injury, where the detection of covert cognition is crucial.

Résumé

L'évaluation du langage chez les patients en état de conscience altérée après une période de coma est rendue difficile par leur répertoire comportemental limité. En outre, la présence de déficits langagiers peut compromettre l'émergence de réponses à des consignes verbales, menant à une sous-estimation de la conscience chez les patients aphasiques. L'introduction propose une revue systématique de la littérature explorant les capacités langagières résiduelles chez les patients en état de conscience altérée selon quatre principaux thèmes : (1) l'évaluation langagière comportementale, (2) l'étude des signes de conscience liés au langage, (3) la détection de réponses à la commande et de capacités de communication latentes via interfaces cerveau-ordinateur, (4) l'activité corticale résiduelle en réponse à des stimulations langagières. Cette revue souligne l'importance de valider de nouvelles évaluations comportementales du langage.

La **Partie expérimentale I** comprend trois études rétrospectives qui ont pour objectif d'explorer les corrélats neuronaux de la réponse à la commande, la verbalisation intelligible et/ou la communication intentionnelle. Ces signes de conscience liés au langage, présents dans l'état de conscience minimale *plus* mais pas dans l'état de conscience minimale *moins*, sont mis en évidence par l'échelle Coma Recovery Scale-Revised (CRS-R). L'**Etude 1** examine le métabolisme cérébral du glucose (via la tomographie par émission de positrons utilisant du fluorodesoxy-glucose, FDG-TEP) et le volume de matière grise (via la morphométrie basée sur les voxels) au sein des deux sous-catégories de l'état de conscience minimale. Nos résultats suggèrent que les fonctions cérébrales au niveau du réseau langagier sont déterminantes pour la récupération des signes de conscience liés au langage. En effet, le groupe en état de conscience minimale *plus* présentait un plus haut métabolisme que le groupe en état de conscience minimale *moins* principalement au niveau du cortex temporal moyen gauche qui est impliqué dans le traitement sémantique. Le gyrus angulaire gauche était aussi fonctionnellement déconnecté du cortex préfrontal gauche pour l'état de conscience minimale *moins* comparé à l'état de conscience minimale *plus*. Aucune

différence significative n'a été montrée entre les groupes pour le volume de matière grise. L'**Etude 2** approfondit ensuite l'étude des fonctions cérébrales sous-tendant cette sous-catégorisation, en évaluant la connectivité fonctionnelle au repos via l'imagerie par résonance magnétique dans des groupes de patients en état de conscience minimale *moins* et *plus*. Une plus haute connectivité a été observée pour l'état de conscience minimale *plus* comparé à l'état de conscience minimale *moins* au niveau du réseau frontopariétal gauche (réseau exécutif de contrôle langagier), en particulier entre le cortex préfrontal dorso-latéral et le cortex fusiforme temporo-occipital gauche. Les groupes d'état de conscience minimale *plus* et *moins* ne seraient toutefois pas distingués par les réseaux associés au traitement auditif, à la perception de l'environnement et à la conscience interne, ni par l'intégration interhémisphérique et l'atteinte structurelle. Enfin, l'**Etude 3** rapporte des données longitudinales de FDG-TEP et morphométrie basée sur les voxels chez 3 patients ayant d'abord été diagnostiqués comme étant en état de conscience minimale *moins*, puis en état de conscience minimale *plus* après avoir récupéré la réponse à la commande. Au second temps de l'étude, ils montraient moins d'hypométabolisme et/ou un plus grand volume de matière grise dans des régions précédemment associées à la conscience interne (précunéus et thalamus), ainsi que dans des régions impliquées dans le langage (noyau caudé et cortex temporal/angulaire gauches). Non seulement le métabolisme de glucose mais aussi le volume de matière grise permettaient donc de différencier l'état de conscience minimale *moins* et *plus* chez un même sujet. Une meilleure caractérisation des corrélats neuronaux des capacités cognitives résiduelles des patients en état de conscience minimale permet de réduire les risques d'erreurs de diagnostic et d'adapter des approches thérapeutiques.

La **Partie expérimentale II** se focalise ensuite sur l'évaluation langagière comportementale réalisée au chevet de patients en état de conscience altérée. De nouveaux outils sont développés et utilisés en comparaison avec la CRS-R, la FDG-TEP et la morphométrie basée sur les voxels. L'**Etude 4** présente l'utilisation de l'outil Cognitive Assessment by Visual Election (CAVE) pour évaluer la reconnaissance d'objets, images, lettres, nombres, mots écrits et couleurs chez 5 patients en état de

conscience minimale ou émergeant de l'état de conscience minimale. Les scores à la CAVE diminuaient en parallèle avec le score total à la CRS-R, établissant un profil cognitif cohérent pour chaque patient. Chacun présentait des altérations cérébrales structurelles et fonctionnelles correspondant à ce profil. Des liens "cerveau-comportement" ont donc pu être suggérés même en présence de lésions cérébrales sévères. Puisque la CAVE ne propose aucune distinction des différents domaines langagiers ni aucun contrôle des variables psycholinguistiques, nous avons finalement élaboré l'outil Brief Evaluation of Receptive Aphasia (BERA). Cet outil évalue la phonologie, sémantique et morphosyntaxe en réception, en se basant sur la sélection visuelle d'une image-cible à côté d'un distracteur spécifique. L'**Etude 5** décrit l'administration de la BERA chez 10 sujets contrôles (afin de s'assurer que leur performance était optimale), 52 patients aphasiques conscients et 4 patients en état de conscience minimale ou en émergeant. Chez les patients aphasiques conscients, la BERA présentait une fidélité intra-/inter-juges et une validité interne et concourrante satisfaisantes. Chez les patients en état de conscience altérée, les scores à la BERA suggèrent la présence de diffultés réceptives pour la phonologie, la sémantique et surtout la morphosyntaxe. Ces résultats peuvent être associés à la neuroimagerie. La BERA permet donc de complémenter la CRS-R dans le diagnostic des états de conscience altérée et de préciser le profil langagier des patients post-coma.

En conclusion, cette thèse est basée sur l'évaluation multimodale de patients en état de conscience minimale (ou en émergeant) et apporte de nouvelles perspectives pour la caractérisation de leurs capacités langagières résiduelles. Nos études permettent également d'aller plus loin dans le désenchevêtrement des altérations de la conscience et du langage après un coma. D'autres études devraient permettre d'optimiser et répéter les évaluations CAVE et BERA chez davantage de patients en état de conscience altérée. Les corrélats neuronaux de déficits langagiers spécifiques devraient également être investigués chez ces patients sévèrement cérébro-lésés, pour lesquels la détection d'une cognition latente est cruciale.

Introduction

The concept of "disorders of consciousness" (DoC) is here introduced, and several studies examining their neural correlates are presented. We then expose the issue of aphasia in DoC patients, and present the up-to-date literature investigating residual language abilities in this population, as assessed by behavioral bedside assessment, electrophysiology and/or neuroimaging.

Based on the following publication:

Aubinet C, Chatelle C, Carrière M, Laureys S, & Majerus S (*in preparation*). Language residual abilities in patients with disorders of consciousness as assessed with behavioral bedside assessment, electrophysiology and neuroimaging: A systematic review.

1. What is consciousness?

Despite all the recent neuroscientific advances, one should admit that the concept of consciousness still remains particularly difficult to define. How can we explain that something so intangible can emerge from our (material) brain? Laureys et al. (2005; 2008) tried to address this issue by considering two specific components: wakefulness, characterized by eye-opening, and awareness, or presence of interactions with the environment and command-following capacity. This definition of consciousness was recently deepened with the proposition of a three-dimension framework including wakefulness, connectedness and internal awareness (Martial et al., 2020). Connectedness reflects the connection to the environment allowing the experience of external stimuli, whereas internal awareness refers to all environment-independent thoughts (e.g., mental imagery, inner speech or mind wandering). These dimensions consequently allow to account for all physiologically (e.g., paradoxical sleep), pharmacologically (e.g., drug effect or anesthesia) and pathologically altered states of consciousness. This thesis will mainly focus on the pathological aspects of consciousness.

2. Disorders of consciousness

Disorders of consciousness (DoC) are characterized by prolonged impaired connectedness and internal awareness following a severe brain damage (Martial et al., 2020). This damage, which could be of traumatic (i.e., motor vehicle accident, falling, etc.) or non-traumatic (i.e., stroke, anoxia, etc.) etiology, initially causes a period of coma (Gosseries et al., 2011).

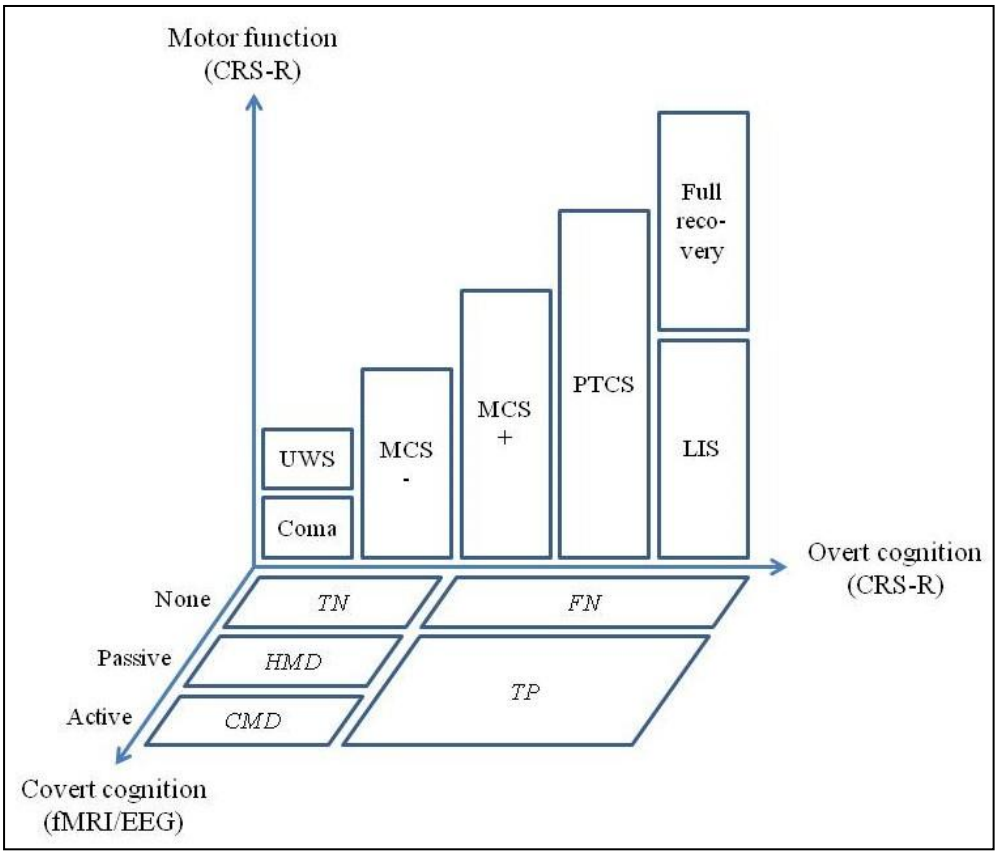

Figure 1.*Diagnosis of disorders of consciousness, adapted from Edlow et al. (2017).UWS: unresponsive wakefulness syndrome, MCS: minimally conscious state, PTCS: post-traumatic confusional state, LIS: locked-in syndrome, TN: true negative, FN: false negative, TP, true positive, HMD: higher-order cortex motor dissociation, CMD: cognitive motor dissociation.*

Patients in coma are neither awake nor aware, but this condition usually lasts no longer than four weeks. When patients awaken but show no signs of awareness of self and surroundings, they are considered as having an unresponsive wakefulness syndrome (UWS; i.e., vegetative state) (Laureys et al., 2010; Multi-Society Task Force on PVS, 1994). When patients recover minimal yet definite behavioral evidence of self or environmental awareness, they are said to be in a minimally conscious state (MCS) (Giacino et al., 2002). The MCS diagnosis has been further sub-categorized into MCS- and MCS+ (Bruno et al., 2011). The most frequent signs of consciousness in MCS- patients are visual fixation and pursuit, automatic motor reactions (e.g., scratching, pulling the bed sheet), and localization to noxious stimulation (Wannez, Gosseries, et al., 2017). Addtionally, MCS+ patients can

follow simple commands (e.g., to look up or move the leg on at least 3/4 commands), intelligibly verbalize (i.e., pronounce at least three words of the consonant-vowel-consonant structure) and/or intentionally communicate (i.e., use a "yes"/"no" code to correctly answer to 2/6-5/6 questions) (Bruno et al., 2011). These patients emerge from the MCS (EMCS or post-traumatic confusional state) once they regain the ability to functionally communicate (i.e., use a "yes"/"no" code to correctly answer to 6/6 questions) and/or use objects such as a comb or a cup (Giacino et al., 2002). Importantly, a differential diagnosis has to be made between DoC and states of profound paralysis causing pseudocoma, namely the locked-in syndrome (LIS) (Bruno, Laureys, & Demertzi, 2013). Figure 1 illustrates the classification of these disorders according to motor function and overt cognition (see also appendix I – supplementary material 1).

Previous literature has shown the importance of accurate diagnosis in DoC patients regarding daily management (i.e., pain treatment or stimulation protocols), end-of-life decisions and prognosis (Chatelle et al., 2016; Demertzi et al., 2011; Thibaut et al., 2017). Nevertheless, establishing an accurate diagnosis is challenging (Andrews et al., 1996; Childs et al., 1993; Gill-Thwaites, 2006; Schnakers et al., 2009; Stender et al., 2014; van Erp et al., 2015), with assessment being compromised by the patients' multiple impairments, in particular motor skills and fluctuating arousal level (Gill-Thwaites, 2006; Schnakers et al., 2009), as well as aphasia (Majerus et al., 2009; Schnakers et al., 2014) and impaired visual abilities (Andrews et al., 1996). Several behavioral scales have been developed to assess patients' level of consciousness. Among them, the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) is currently considered the most sensitive validated diagnostic tool (Seel et al., 2010). This scale includes 23 items divided in 6 sub-scales: auditory, visual, motor, oro-motor/verbal, communication and arousal, each assessing different items of increasing complexity. Some of the items are diagnostic criteria for MCS (e.g., visual pursuit, automatic oriented motor reactions or response to command) and EMCS (i.e., functional communication and/or use of objects).

Diverse neuroimaging techniques have been developed due to the difficulty to behaviorally objectifying signs of consciousness and cognition in this group of severely brain-injured patients (Gosseries et al., 2016). Several studies have emphasized the role of state networks encompassing associative cortices on the midline (internal awareness network or default mode network – DMN) and on the convexity (external awareness network or frontoparietal network) for the emergence of consciousness (Laureys et al., 2004; Vanhaudenhuyse et al., 2011). In particular, studies using resting-state functional magnetic resonance imaging (fMRI), a non-invasive technique investigating the spontaneous temporal coherence in blood-oxygen-level dependent (BOLD) fluctuations (Raichle et al., 2001), have shown that DMN functional connectivity increases linearly to the level of consciousness, from coma to healthy consciousness (through UWS, MCS and EMCS) (Demertzi et al., 2015; Di Perri et al., 2016; Vanhaudenhuyse et al., 2011). In a similar manner, functional connectivity of the frontoparietal network has shown to be impaired in DoC patients, and this impairment is more severe in the UWS than in MCS (Crone et al., 2013). Furthermore, the frontoparietal network, classically considered as an executive control network (Reineberg & Banich, 2016; Smith et al., 2009), has been subdivided into the right frontoparietal network, known to be involved in somesthesic processing and nociceptive perception (Laird et al., 2011; Smith et al., 2009), and the left frontoparietal network, considered to be related to executive language processing (Geranmayeh, Leech, & Wise, 2016; Laird et al., 2011; Smith et al., 2009) and to act as a "semantic control system" by interacting with a left perisylvian network and with the DMN (Xu et al., 2016).

Recent research has further highlighted the role of DMN between-network anticorrelations (i.e., anticorrelations between the DMN and frontoparietal network) in the recovery of consciousness (Di Perri et al., 2016). The strength of DMN (between-network) anticorrelations is positively associated to the level of consciousness ranging from UWS to healthy consciousness. In particular, only EMCS patients and healthy control subjects showed these DMN between-network anticorrelations. Patients in altered states of consciousness had atypical positive

correlations between the two networks, suggesting that anticorrelations characterize the level of consciousness involved in functional communication and object use. These findings imply that DMN anticorrelations may play an important role in inter-network information integration during consciousness by allowing for alternation between extrospectively-oriented and introspectively-oriented modes of function (Fransson, 2005); this aspect has also been considered to be indicative of subjectivity or conscious awareness (Demertzi et al., 2013).

Similarly, thalamocortical connections were shown to play a crucial role in patients' behavioral profile and complex information integration sustaining conscious awareness, by means of both structural and neurophysiological studies (Estraneo et al., 2016; Kim et al., 2012; Zheng et al., 2017).

Dissociations between the gold standard CRS-R diagnosis and neuroimaging results may appear, and a diagnostic label of 'non-behavioral MCS' or MCS* was suggested to account for patients with relatively preserved consciousness brain networks despite the absence of behavioral signs of consciousness (Gosseries, Zasler, & Laureys, 2014). As shown in figure 1, Edlow et al. (2017) classified patients according to the presence of behavioral diagnosis of coma, UWS or MCS either with command-following on brain-computer interfaces (i.e., 'cognitive-motor dissociation') or with association cortex response to language or music stimuli (i.e., 'higher-order cortex motor dissociation'). Other studies further discussed the underlying mechanisms of cognitive-motor dissociation (Fernández-Espejo, Rossit, & Owen, 2015; Schiff, 2015), providing evidence for a selective interruption of the excitatory coupling of thalamus and motor cortex. As covert cognition in DoC patients reveals the presence of residual language processing, these cognitive-motor and higher-order cortex motor dissociations will be developed in sections 6. and 7.

3. Assessment of language in patients with disorders of consciousness

One of the most common questions regarding DoC patients is "Can they understand us?" Language assessment in these patients is however complicated by their limited behavioral repertoire. The difficulty in answering this question is even more important as language disorders like receptive aphasia (i.e., involving language comprehension deficits) represent one of the major issues in the assessment of consciousness in such severely brain-injured patients (Majerus et al., 2009). Indeed, the presence of language deficits might prevent consistent responses to verbal instructions, leading to an underestimation of consciousness in aphasic patients. This "bias of aphasia" on the use of CRS-R was investigated by assessing 24 aphasic conscious post-stroke patients (Schnakers et al., 2014). In this study, an underestimation of the level of consciousness was observed in half of patients with global aphasia (54%), who could erroneously have received the diagnosis of MCS according to this test.

The same authors argued that behavioral scales estimating patients' level of consciousness are obviously limited in ensuring a reliable assessment of specific cognitive functions like language. As illustrated in figure 2, if the CRS-R allows the detection of language-related signs of consciousness (i.e., distinguishing MCS- and MCS+ patients), patients' performance is however determined by many other motor or cognitive functions. Furthermore, these items do not assess language-specific functions as they are classically presented in language models such as Patterson & Shewell (1987).

To document the presence of aphasia in DoC patients, Majerus et al. (2009) suggested the use of multimodal assessment protocols, combining bedside evaluations, neuroimaging and electrophysiology. Some authors focused on the language-related signs of consciousness and their neural correlates in this population

(e.g., Bruno et al., 2012), while others rather used fMRI or electroencephalography (EEG) to evidence the presence of covert residual language (e.g., Coleman et al., 2009; Edlow et al., 2017; Harrison & Connolly, 2013; Owen & Coleman, 2008).

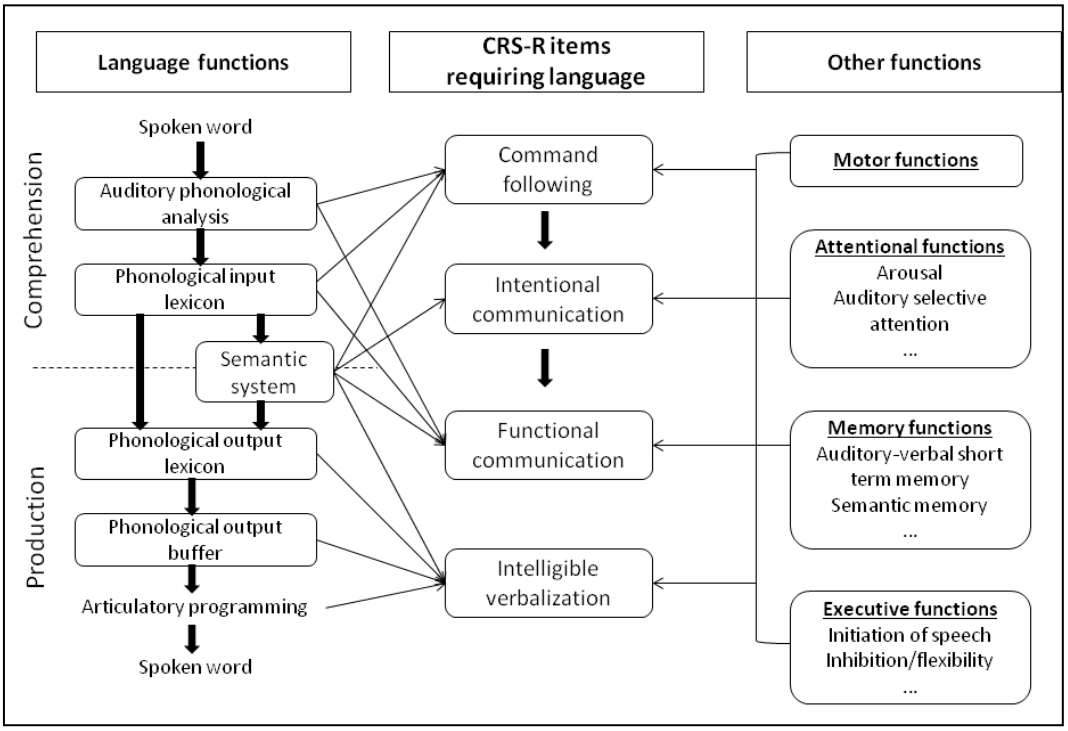

Figure 2. *Influence of language and other functions on the administration of Coma Recovery Scale-Revised (CRS-R) language-related items. On the left: language model adapted from Patterson and Shewell (1987) in the center: the four CRS-R items directly requiring language residual abilities; on the right: motor and cognitive functions impacting patients' CRS-R performance.*

In the next sections, we aim to explore the literature investigating residual language abilities (i.e., speech comprehension and/or production) in DoC patients after severe brain injury, as assessed by behavioral language assessment, neuroimaging and/or electrophysiology. In sum, 75 studies were selected (among 806 studies), described and analyzed during the process of a systematic review (methods and results are reported in appendix I – supplementary material 2 to 4). A synthesis of all results is presented.

4. Behavioral language assessment

According to our systematic research, the literature described very few attempts of behavioral language assessments. For instance, communication abilities may be listed either using the Loewenstein Communication Scale (Borer-Alafi et al., 2002) or the Individual Nonverbal Communication Rating Scale (Rasmus et al., 2019). The first one scores the patient's mobility, respiration, visual responsiveness, auditory comprehension (response to noise and voice, reaction to simple and complex verbal tests), verbal communication (use of speech articulators, basic speech, articulation, rhythm/fluency and message quality) and alternative communication (need for outside assistance, use of body parts, initiative, speed and message quality). The second one combines patients' observation, family interviews, scores using the Glasgow Coma Scale (Teasdale & Jennett, 1974) and estimation of preverbal, verbal and interpersonal communication, as well as creative expression. All these criteria were estimated with reference to emotional level, language and cognitive level or social level. This second study did not however present concrete definitions or examples of items. Even more importantly, both studies only used the Glasgow Coma Scale to estimate patients' level of consciousness, leading to uncertain DoC diagnoses.

A third study also presented an estimation of residual language based on patients' bedside observation, the "Chiba score", as compared to neuroimaging measurements (Yamaki et al., 2018). The authors basically observed more residual language abilities (especially in production) in association with an increased brain glucose metabolism in 45 DoC patients, including 8 UWS and 20 MCS patients.

Murphy (2018) finally presented the Cognitive Assessment by Visual Election (CAVE) in a recent pilot study. This scale is composed of 6 subscales evaluating recognition of objects, pictures, numbers, letters, written words and colors in DoC patients, and consequently involves language comprehension. Results were

promising as they showed high levels of inter-rater and test-retest reliability. The CAVE does however not allow the distinction of various domains of language nor the control of psycholinguistic effects.

5. Language-related signs of consciousness

Several studies primarily proposed recommendations regarding the detection of language-related behaviors as assessed by the CRS-R: auditory localization was found to be more often elicited using the subject's own name rather than a neutral sound (Cheng et al., 2013), whereas command-following was more consistently documented using the Individualized Quantitative Behavioral Assessments (Whyte, DiPasquale, & Vaccaro, 1999) which involves the administration of 4 to 8 command trials (Day, DiNapoli, & Whyte, 2018). Note that both studies presented high risk of bias, in particular for the CRS-R reference standard involving circularity.

Yet, most studies rather focused on the neural correlates of CRS-R language-related items (i.e., command-following, intelligible verbalization and intentional communication), using structural and/or functional brain imaging, as well as EEG. With regard to functional aspects, Bruno et al. (2012) used fluorodeoxyglucose positron emission tomography (FDG-PET) and observed a higher brain glucose metabolism in left-sided cortical areas including language-related areas, as well as a better connectivity between Broca's region and the rest of the language network, in MCS+ compared to MCS-. Other authors used EEG and distinguished DoC patients who are able to respond to commands from those who are not. In those who recovered this ability, they found an increase in central gamma and posterior (centro-occipital) alpha power, as well as in complexity measures such as alpha permutation entropy (Claassen et al., 2016).

Using structural MRI, Guldenmund et al. (2016) performed a voxel-based morphometry (VBM) analysis in 8 MCS- and 37 MCS+ patients. Results showed

more preserved grey matter volume in left language-related areas (i.e., middle temporal gyrus, superior temporal gyrus and inferior frontal gyrus) in MCS+ compared to MCS-. They however used a statistically liberal threshold (uncorrected $p = 0{,}01$), which increases the risk of bias with regard to the index test. Zheng et al. (2017) rather used diffusion tensor imaging (DTI) and compared 7 MCS- and 8 MCS+ patients. An increased structural support was shown for thalamo-premotor and thalamo-temporal (possibly including language-related regions) connectivity in MCS+ compared to MCS-.

6. Detection of command-following by means of brain-computer interfaces

Given the extent of brain lesions in DoC patients, the persistence of severe motor impairments is almost inevitable, possibly preventing patients to demonstrate response to commands and communication attempts. Numerous studies therefore endeavored to circumvent motor impairments by means of brain-computer interfaces, where patients are required to exert mental response to command, in contrast to passive paradigms (Hauger et al., 2017) or rest. Such 'active paradigms' most often include motor imagery tasks, which require rehearsing or simulating a given action (e.g., imagine playing tennis). The presence of covert command-following is observed when DoC patients' pattern of brain activation is similar to those of healthy control subjects, consequently revealing the presence of cognitive-motor dissociation.

a. fMRI as brain-computer interface

Some studies exclusively used fMRI imagery tasks to observe covert command-following, but only a limited proportion of patients successfully fulfilled these tasks. In a single case study describing an unresponsive patient with covert command-following after traumatic brain injury (TBI), Owen et al. (2006) firstly showed activation to tennis imagery (i.e., command "imagine you play tennis") in supplementary motor area, whereas activation to spatial navigation imagery (i.e., command "imagine you walk into your house") was found in parahippocampal gyrus, posterior parietal lobe and lateral premotor cortex. Using 'hand squeezing' and 'tennis playing' tasks, Bodien et al. (2017) further showed significant responses in 1/7 and 2/7 unresponsive patients, respectively. Bardin et al. (2011) additionally used swimming and tennis motor imagery tasks to test for both command-following and communication skills. Three out of 6 patients (2/5 MCS and 1/1 with locked-in syndrome; LIS) performed the command-following task and 1/5 MCS patient interestingly showed activation in multiple choice communication. Four different tasks were directly compared by Liang et al. (2014): motor ("imagine playing tennis"), navigating ("imagine navigating your home"), faces ("imagine familiar faces") and counting ("count up from 10 by 7's" versus "rest"). They found that 1/3 UWS and 2/2 MCS patients had partial overlap with control activations for some tasks ('navigating' for one of them, 'counting' for the UWS patient and one of the MCS patients, and 'faces' for the other MCS patient). No communication attempt could however be observed with the question-answer task. Other case studies showed higher brain activation in DoC patients who were asked to count some targets compared to passive listening or rest (Monti, Coleman, & Owen, 2009; Naci & Owen, 2013). Finally, according to Naci et al. (2018), 6/11 DoC patients followed task commands (i.e., to count target words) by willfully modulating their brain activity as requested, and 2/11 presented a cognitive-motor dissociation profile (i.e., behavioral diagnosis of UWS that was inconsistent with their positive fMRI results). Command-following capacities (including sentence comprehension) could thus emerge in some DoC patients by using several fMRI imagery and counting tasks.

Besides, the use of fMRI visual recognition tasks has also been suggested (Coleman et al., 2009). A single-case study from Monti et al. (2013) for example required from the patient to selectively fixate one image among two images (i.e., a face versus a house). This approach revealed appropriate brain activations, undistinguishable from those seen in healthy subjects. The patient was indeed able to focus on one of these two competing stimuli, and switch between them on command. Interestingly, Rodriguez-Moreno et al. (2010) employed fMRI during covert picture-naming (as a command-following task) with 10 patients with and without behavioral evidence of awareness. This task normally recruits activity in the superior temporal gyrus (including Wernicke area), inferior frontal gyrus (including Broca area) and medial frontal gyrus. They observed complete network activations for both the LIS and EMCS patients, for 2/5 MCS patients (both MCS+ patients) and 1/3 UWS patients, as well as at least partial activation for 5/5 MCS patients (including 1 MCS- patient) and 2/3 UWS patients. A general correspondence was also demonstrated between the integrity of the language-specific network and the CRS-R assessment. These findings importantly highlighted the presence of residual visual recognition in a large proportion of DoC patients.

The literature also includes several multimodal studies aiming at covert command-following detection. As previously mentioned, Fernandez-Espejo et al. (2015) performed DTI analyses on a patient with covert command-following (i.e., appropriated brain activations following fMRI motor imagery commands) compared to another fully unresponsive patient and to healthy subjects. The results showed a selective structural disruption in the fibers connecting the thalamus and primary motor cortex in the first patient, but not in the second one, hinting at the importance of this tract in reappearance of residual language abilities. In another study combining fMRI and EEG, Forgacs et al. (2014) showed typical fMRI brain activations regarding motor and visuo-spatial tasks in 4/26 DoC patients (i.e., 3 MCS and 1 EMCS patients). These patients were also found with preserved EEG organization during wakefulness and spindling activity during sleep, as well as relatively preserved brain glucose metabolism. Braiman et al. (2018) further showed

appropriate activations using fMRI motor imagery tasks in 10/21 DoC patients (including patients without behavioral command-following). All 10 patients showed no differences using EEG in natural speech envelope latencies compared to healthy subjects. Bekinschtein et al. (2011) rather selected patients on the basis of EEG word-related activity, and then showed using fMRI that 2/5 patients correctly activated the dorsal premotor cortex contralateral to the hand they were asked to move. Using a right hand squeeze imagery task in acute settings, Edlow et al. (2017) finally revealed fMRI-based motor imagery responses in 7/15 patients (4/8 with no behavioral evidence of language) and EEG-based motor imagery responses in 3/13 patients (0/8 with no behavioral evidence of language). Consequently, fMRI and EEG responses to motor imagery were shown to be 42% sensitive and 50% specific, and 33.3% sensitive and 100% specific, respectively, for behavioral evidence of language in DoC patients. Prognostic cues were provided as most patients with cognitive-motor dissociation recovered beyond a confusion state by 6 months.

Overall, the literature showed (covert) command-following capacity in several DoC patients by means of fMRI and active tasks involving motor imagery (e.g., command “imagine you play tennis”), counting (e.g., command “count the target word”) or visual recognition (e.g., command “look at the house”), which could also allow communication attempts. Some patients seem to respond better to one or other of these tasks, and the presence of cognitive-motor dissociation would be linked to a disconnection between the thalamus and motor cortex. The ability to cortically respond to commands was also associated to EEG and brain glucose metabolism measurements. Finally, fMRI responses were shown to be more sensitive but less specific than EEG responses, such as presented in the next section.

b. EEG as brain-computer interface

Given the difficulty to use fMRI in clinical settings, several studies intended to develop EEG paradigms aiming at the detection of covert command-following.

Motor imagery tasks were also used in EEG paradigms. For instance, Curley et al. (2018) employed tasks such as 'tennis' ("imagine you swing a tennis racket with your hand"), 'hand' ("imagine you open/close the right (left) hand"), 'navigate' ("imagine you walk through your house), and 'swim'. Despite a broad heterogeneity in patient-generated EEG responses, they found EEG evidence of command-following in 21/28 DoC patients, 9 of whom were behaviorally unresponsive. Note that only 9/28 patients exhibited fMRI responses to command, supporting the added utility of electrophysiological detection. Additionally, according to Goldfine et al. (2011), 1/2 MCS and 1/1 LIS patients showed evidence of swimming imagery task performance, though with patterns of spectral change different from healthy subjects. In a case study, Forgacs et al. (2014) also described a behaviorally unresponsive patient who showed EEG-based covert command-following in presence of normal brain glucose metabolism and electrical activity across the entire anterior forebrain. Furthermore, other authors recently used motor commands ("keep/stop opening the hand") and obtained appropriate EEG responses in 16/104 behaviorally unresponsive acute patients (Claassen et al., 2019). This paradigm is of prognostic value as 8 out of these 16 patients (50%) and 23 out of the other 88 patients (26%) recovered behavioral command-following before discharge. Moreover, at one year post-injury, 7 out of these 16 patients (44%) and 12 out of the other 88 patients (14%) were able to function independently for 8 hours.

The use of counting commands was further described by various authors. Annen et al. (2018) and Guger et al. (2018) respectively reported covert command-following in 1/12 and 2/12 unresponsive patients when they were asked to count vibro-tactile stimuli. The patient with covert command-following in the first study presented higher glucose metabolism in the language network as compared to the other 11 patients. In a mismatch negativity (i.e., component of event-related potentials [ERPs] to an odd stimulus in a sequence of stimuli) paradigm, Faugeras et al. (2012) acquired 65 recordings by asking patients to count the deviant stimuli. In this counting condition, the recordings were shown with global mismatch negativity in 2/24 UWS and 4/28 MCS patients and they suggested that the ERP "global

effect" could be a specific marker of consciousness in non-communicating patients. Using the subject's own name (SON) as stimulus, Hauger et al. (2015) also showed larger P3 component in 4/20 patients (3 MCS+ and 1 MCS- patients) when they were asked to listen for change in pitch compared to rest, whereas higher P3 amplitudes were observed in 9/20 patients (4 MCS+ and 5 MCS- patients) in the SON counting condition compared to passive listening. A distinction between MCS- and MCS+ was proposed with 67% sensitivity. Similarly, Risetti et al. (2013) observed in 3/3 MCS patients an increased amplitude for P3 component in 'SON counting', which correlated in each patient with the CRS-R auditory sub-score. Lastly, a 4-choice auditory oddball paradigm was described by Lulé et al. (2013), asking patients to count the number of times a verbal target ("yes" or "no") appears. The results revealed command-following in 1/13 MCS and 1/2 LIS patients, but communication was only performed by the LIS patient. The literature on EEG therefore presented possible command-following capacity in DoC patients using counting commands with vibro-tactile stimuli, sounds, SON or verbal targets.

Other studies however reported less success in detecting covert command-following by means of EEG imagery tasks such as 'hand moving'. Indeed, Höller et al. (2013) detected evidence of command-following in 5/14 patients but only using an uncorrected threshold, leading to a high risk of bias. Moreover, Hinterberger et al. (2005) found such evidence in 1/5 patient, but this patient was actually able to move the hand. Finally, Chatelle et al. (2018) presented an EEG-based brain-computer interface which is feasible in DoC patients even in intensive care units; they however recognized that it was still unreliable.

EEG visual recognition tasks have finally been proposed in order to detect covert command-following in DoC patients. Indeed, Pan et al. (2014) presented two pictures to 4 DoC patients: one was the patient's own photo whereas the other one was unfamiliar (i.e., photo of an unknown person). The brain-computer interface system identified the photo on which the patient focused on with both P300 and steady-state evoked potential responses. They observed covert ability to selectively fixate either their own photo or the unfamiliar photo on command in 1/4 UWS and

1/3 MCS patients. Two additional patients (1 UWS and 1 MCS) showed appropriate fixations only for their own photo.

Using EEG and ERPs, DoC patients thus showed (covert) command-following capacity with tasks using motor imagery (e.g., command "imagine you move the left hand"), counting (e.g., command "count the sounds") and visual recognition tasks (e.g., "look at your own photo"). The ERP "global effect" or P3 amplitudes (in SON counting conditions) were particularly highlighted as markers of consciousness. Some of these paradigms however remain unreliable in this challenging population. Other inventive brain-computer interface devices were therefore adopted to detect covert command-following.

c. Other brain-computer interfaces

Habbal et al. (2014) employed electromyography and asked DoC patients to move the hand, move the leg or clench the teeth. They found a significant response to these commands in 1/10 behaviorally unresponsive patient, as well as in 3/20 MCS+ patients. Vassilieva et al. (2019) further assessed the feasibility of automated pupillometry for the detection of response to counting and calculating commands, in a convenience sample of 'neurological patients'. They found that 17/43 patients fulfilled the pre-specified criteria, including the MCS- patient with behavioral evidence of visual pursuit. A last surprising study used a "sniff controller" setting and asked DoC patients to stop a music sequence by sniffing deeply through a nose cannula. Such setting allowed to detect covert command-following in 1/14 MCS- patient, who was able to willfully modulate his breathing pattern to answer the command on 16/19 trials (84%) (Charland-Verville et al., 2014). These interesting devices would however need to be further investigated to evidence their validity in DoC patients.

In conclusion, most of the present studies provided important evidence of residual language comprehension abilities in some DoC patients by detecting covert command-following and cognitive-motor dissociation, which could also be of prognostic value. According to a recent meta-analysis, approximately 15% of patients who are behaviorally diagnosed as UWS would possess some capacity to respond to commands (Kondziella et al., 2016). The included studies however recruited convenience samples (i.e., high risk of bias regarding the population), and most of them remained unclear on several methodological aspects such as blinding processes and interval between behavioral assessments and brain-computer interface performance. Yet, we reported low concerns regarding the applicability of patient selection, index test and reference standard to our review question.

7. Measure of cortical activity in response to language stimulation

Another way to circumvent patients' severe motor impairments is the use of neuroimaging- or EEG-based language passive paradigms. In this section, we review the studies using language stimuli which have shown that some DoC patients demonstrate association cortex responses despite absent behavioral evidence of language production and comprehension (i.e., higher-order cortex motor dissociation).

a. Speech and noise

Several studies examined brain responses of DoC patients when differentiating intelligible speech and noise. For example, Coleman et al. (2007) and Coleman, Martin et al. (2009) used fMRI and compared responses to sentence versus noise

listening, respectively in 14 patients (7 UWS, 5 MCS and 2 EMCS) and 41 patients (22 UWS and 19 MCS). Both studies found neural correlates of speech comprehension in a subset of unresponsive patients. The first one showed 5/14 patients (3 UWS and 2 MCS+) with significant temporal lobe responses in the speech versus noise perception contrast, while the second demonstrated such cortical activity in 19/41 patients (7 UWS, 8 MCS- and 4 MCS+). The authors revealed a wide variation in the extent of these neural responses, from extensive bilateral superior temporal area to reduced posterior part of the temporal lobes. The other patients may be able to perform some low-level auditory processing, but neural responses are either too weak or too variable to be statistically reliable. These two studies present high risk of bias, given the lack of pre-specified threshold. Similarly, several studies showed contrasts between noise and speech by means of EEG (Erlbeck et al., 2017; Kotchoubey et al., 2005a; Sergent et al., 2017). For example, Beukema et al. (2016) showed that the ERPs elicited by words were significantly more negative than the ERPs elicited by noises across midline fronto-central-parietal scalp in healthy subjects, and 7/16 patients (3 UWS and 4 MCS) showed such speech-noise differences. There was however no difference in auditory processing between UWS and MCS groups.

Higher-order cortex motor dissociation was defined as behavioral unresponsiveness with preserved cortical response to speech (Edlow et al., 2017). The cortical responses to speech compared to noise in DoC patients were shown to range from extensive bilateral superior temporal area to reduced posterior part of the temporal lobes. Using EEG, they would be more negative than the ERPs elicited by noise across midline fronto-central-parietal scalp. These findings suggest a relative preservation of (at least) the earliest language component (i.e., auditory phonological analysis; figure 2) (Patterson, 1987), which enables the detection of speech.

b. Intelligible and less intelligible speech

Brain activations following the listening of sentences of high, medium or low intelligibility were examined. Owen et al. (2005) used $H_2{}^{15}O$ PET in a UWS patient who was presented either normal spoken language (i.e., declarative English sentences) or speech in noise (i.e., distortion generated by adding a continuous pink-noise background to these sentences at three signal-to-noise ratios). Such less intelligible speech has disrupted spectral and temporal properties, but preserved duration, amplitude and overall spectral composition of the original. The analyses revealed preserved consistent responses in predicted regions of auditory cortex (i.e., left superior and middle temporal gyri) in response to intelligible speech, which was thus better detected than less intelligible speech.

Other similar studies were based on fMRI and found more extended cortical responses to forwards compared to backwards speech, encompassing higher areas such as superior temporal and angular gyri. First, Schiff et al. (2005) employed auditory narratives of familiar events presented by a familiar person (forwards and backwards). For both MCS patients, auditory stimulation with these personalized narratives elicited cortical activity in the superior and middle temporal gyrus, which is in line with healthy subjects. These subjects however showed similar activation when the narratives were presented as a time-reversed signal without any linguistic content (i.e., backwards speech), whereas the MCS patients had markedly reduced responses. This could reflect a failure of patients to "recognize" the backwards stimuli as speech. Fernandez-Espejo et al. (2010) further used 20 second long spoken narratives (again forwards and backwards) regarding everyday events to examine one UWS patient by means of fMRI, as well as DTI. The expected higher activation to forwards speech was shown in the left superior and middle temporal gyrus, although using a reduced statistical threshold (i.e., index test high risk of bias). Besides, they found a relative preservation of the arcuate fasciculus and global normal-appearing white matter. A neuropsychological assessment also revealed recovery of receptive linguistic functioning by 12 months post-ictus. More recently, Edlow et al. (2017) showed that 9/16 healthy subjects and 6/16 patients with or

without behavioral evidence of language demonstrated more superior temporal gyrus activation to forwards language (50% sensitive and 62.5% specific) compared to backwards language. Finally, Tomaiuolo et al. (2016) described, in a longitudinal single case study, the progression from UWS to EMCS along with corresponding task-related neural responses. Specifically, while in a MCS (but not with UWS), the patient showed selective recruitment of the left angular gyrus when he listened to forwards speech compared to backwards speech. In addition, this patient showed increased response in the language network and greater deactivation in the DMN following progression to the MCS.

The presence of higher-order cortex motor dissociation was shown in several DoC patients when listening to intelligible compared to less intelligible speech. In the first condition, more extended and superior activations were described in the superior and middle temporal gyri and in the left angular gyrus. A relative preservation of the phonological input lexicon (Patterson, 1987), allowing identification of familiar words, could here be hypothesized (figure 2). DoC patients could fail to recognize backwards stimuli as speech while presenting normal responses to forwards speech, which were associated with preserved white matter particularly in the arcuate fasciculus.

c. Word semantic relatedness and lexical effects

At the word level, some authors focused on semantically related versus unrelated word contrasts and showed different EEG responses in a certain proportion of patients. In the study of Beukema et al. (2016), only 1/16 patients (i.e., MCS-patient) showed the N400 effect when asked to think if words are related or unrelated, while Kotchoubey et al. (2005) found cortical responses in all UWS patients (n = 38) with a background EEG activity > 4 Hz. The passive listening of related versus unrelated word pairs further allowed Erlbeck et al. (2017) to solely identify an N1 (i.e., simple processing mechanism considered as prerequisite for more complex processes and later components like N400) in 1/19 patient who was

diagnosed with UWS. Finally, Rohaut et al. (2015) showed an N400 effect in 6/29 patients (5/14 MCS and 1/15 UWS) and a late positive component in 9/29 patients (8/14 MCS and 1/15 UWS). The only three patients presenting both effects were MCS, and two of them regained consciousness and language.

In an innovative multimodal study using EEG and neuroimaging techniques, Nigri et al. (2017) investigated the neural correlates of lexical residual abilities in DoC patients by means of an fMRI priming task including presentation of word pairs. These stimuli pairs were constituted of semantically related words, semantically unrelated words, word-pseudoword and pseudoword-pseudoword pairs. Using various contrasts, the authors assessed, at the single subject-level, the low-level auditory effect, the lexical effect, the pseudoword effect, the semantic relatedness effect and the semantic unrelatedness effect. They found significant activation in at least one of the contrasts in 8/11 patients (4/7 MCS and 4/4 UWS), including 7/8 (4 MCS and 3 UWS) with low-level auditory effect. Four patients (3 MCS and 1 UWS) showed a pseudoword effect in the left or right superior temporal gyrus, left middle temporal gyrus and/or left or right inferior frontal gyrus; two patients (1 MCS and 1 UWS) showed a lexical effect in the right inferior frontal gyrus and left middle temporal gyrus; one UWS patient showed a pseudoword effect in the inferior frontal and temporal gyri, as well as a semantic relatedness effect in the middle temporal gyrus and angular gyrus. The spatial extent of these neural responses was variable among patients. No significant activation was however detected with regard to the semantic unrelatedness effect. All the included patients showed EEG responses to auditory stimuli, and all except one UWS patient showed a significant glucose metabolism in some brain regions, in which the significant fMRI activations were also present. To our knowledge, this research is the only one proposing an evaluation of specific lexical processes in DoC patients. Yet, as in most of the included studies, the blinding process and interval between behavioral and language assessments remained unclear.

In sum, an EEG N400 effect (at least late positive component or other less complex processes) was evidenced here in healthy subjects and some DoC patients

using semantically related versus unrelated words. Such contrasts were examined using fMRI and differentiated responses were obtained in an UWS patient in the middle temporal gyrus and angular gyrus. Pseudoword and lexical effects in several DoC patients further encompassed the bilateral superior temporal and inferior frontal gyri, as well as the left middle temporal gyrus. Residual abilities regarding the semantic system (figure 2) could therefore be described in several DoC patients.

d. Sentences and narratives

Several neuroimaging studies contrasted sentences of low and high ambiguity, i.e., including words of same pronunciation with various meanings (homonyms or homophones), possibly highlighting residual semantic processing in DoC patients. For instance, the case study of Owen et al. (2005) utilized either sentences containing at least two ambiguous words (e.g., there were *dates* and *pears* in the fruit bowl) or sentences that had the same number of words and syntactic structure but containing words with minimal ambiguity (e.g., there was beer and cider on the kitchen shelf). A preliminary fMRI examination revealed partially intact posterior inferior temporal lobule responses to semantically ambiguous stimuli, which are known to tap higher aspects of speech comprehension. In both studies of Coleman et al. (2007; 2009), 3/14 (2 UWS and 1 MCS+) and 4/41 (2 UWS, 1 MCS- and 1 MCS+) patients showed evidence of intact semantic processing when comparing the listening of low and high ambiguity sentences, in the left inferior frontal gyrus (including for the UWS also described in the study of Owen et al., 2005) or in the temporal lobule. The level of auditory processing revealed by fMRI also correlated strongly with the patient's subsequent behavioral recovery, six months after the scan. Coleman, Bekinschtein et al. (2009) also used this task in a single MCS- patient, in combination with EEG, DTI and behavioral assessment. A hierarchical fMRI auditory paradigm suggested perception of sound and speech but no evidence of speech comprehension or ability to respond to command as assessed using motor imagery tasks. The EEG confirmed that he retained a preserved neural axis

supporting hearing, and suggested that he was able to create a basic memory trace. Furthermore, DTI data suggested that the level of cortical integration required for higher-level tasks (investigated using the Sensory Modality Assessment and Rehabilitation Technique) was no longer sufficient. Evidence of residual semantic processing was thus reported in several post-comatose patients, including UWS patients, by contrasting sentences of low and high ambiguity

Other EEG studies presented to patients some sentences, which were either congruous (i.e., including a semantically related final word) or incongruous (i.e., unrelated final word). The use of such contrasts may also highlight the presence of residual semantic processing in DoC patients. For example, Schoenle et al. (2004) showed, in a sample of 120 post-comatose patients, that most patients who recovered beyond the vegetative state were able to distinguish both sentence types (N400 in 90% of those patients) and a substantial proportion (77%) of patients in "near vegetative state" (i.e., with one criteria such as habituation, eye fixation, visual pursuit or orienting reactions) produced an N400 in one of three forms. Importantly, 39% of patients in vegetative state (i.e., UWS) showed some form of N400 waves, implying residual semantic capacities. The authors concluded that ERPs provide valuable information about brain-injured patients whose clinical conditions often do not allow a true assessment of their cognitive capabilities. This is in line with the study of Kotchoubey et al. (2005), where responses of DoC patients to incongruous last words occurred significantly above chance, though less frequently than in patients with severe brain injury who were conscious. The results further suggested that remaining cortical information processing (including semantic processing) would be a consistent finding in a subset of UWS patients with preserved thalamocortical feedback connections. Moreover, Balconi et al. (2013) found increased N400 peak amplitude within the fronto-central cortical areas in response to incongruous final words for 20/20 healthy subjects, 10/10 UWS and 8/8 MCS patients. They also concluded that such response was not abolished in DoC patients, even though they presented delayed peaks compared to healthy controls. In a second study, Balconi et al. (2015) showed similar increased N400 peak amplitude in

response to incongruous final words for 7/7 UWS and 11/11 MCS patients, and the UWS patients showed a delayed N400 compared to MCS patients. Note that the behavioral scores correlated with the ERP modulation (i.e., peak amplitude and latency). Besides, other studies failed to show the N400 response to incorrect ending words. Indeed, Erlbeck et al. (2017) could only identify a late positive complex in 2/19 patients, both with UWS.

Two additional EEG cohort studies used the same paradigm to document patients' recovery. Formisano et al. (2019) found the N400 component in response to the ill-formed sentences with centro-parietal topography in 9/10 healthy subjects, as well as in 9/14 patients (4 UWS and 5 MCS; 64%), none of them having left-sided lesions. No significant N400 was retrospectively detected in those EMCS patients who showed aphasia at the follow-up, and the presence or absence of this component was consistent with brain lesion side and predicts the recovery. In a prospective longitudinal cohort study, Steppacher et al. (2013) identified an N400 in 16 (visual inspection) to 32% (use of specific algorithm) of UWS patients (n = 53) and 21 (visual inspection) to 32% (use of specific algorithm) of MCS patients (n = 39). Importantly, the presence of N400 was highly related to subsequent recovery. Nevertheless, the reference standard was the Coma Remission Scale (not the gold standard CRS-R) and it was not administered on the day of the EEG assessment, leading to high risk of bias.

In the same line, Schabus et al. (2011) employed sentences in three conditions: related word (e.g., the opposite of black is *yellow*), unrelated word (e.g., the opposite of black is *nice*) or antonym (e.g., the opposite of black is *white*). MCS patients (but not UWS patients) showed specific upper alpha (10-12 Hz) event-related synchronization and desynchronization responses to unrelated words and antonyms respectively.

Alternatively, Kotchoubey et al. (2013) proposed the use of factually correct versus incorrect short sentences in an fMRI research. Significant brain responses to the incorrect compared to the correct sentences were found in 16/55 patients (11 UWS including 2 full responders and 5 MCS again including 2 full responders), and

mainly recorded in left-sided language-related areas such as Broca and Wernicke areas. These 16 responders had a significantly longer time since injury than the 39 non-responders.

Another interesting study from Naci et al. (2018) suggested the use of specific narratives in an inventive fMRI passive paradigm including 11 DoC patients who were divided in "DoC+" (i.e., covertly aware patients) and "DoC-" (i.e., no command-following). During the broadcast of a plot-driven narrative from the kidnapping scene of the movie "Taken" (5 minutes), the DoC+ group showed down-regulation of the connectivity of auditory network and frontoparietal (auditory-dorsal attention and executive control networks) and significantly differed from the DoC- group who did not show this effect. The functional differentiation between the auditory and frontoparietal systems decreased significantly relatively to the level of consciousness. Interestingly, stronger functional differentiation between these systems in response to speech stimulation also predicted higher intellectual abilities in healthy subjects during conscious cognition (higher verbal acuity scores in independent cognitive testing battery).

As exposed here, various studies investigated DoC patients' cortical responses to sentence processing. Specifically, the contrast between sentences of low and high ambiguity in these patients mainly involved the left inferior frontal gyrus and temporal lobule using fMRI. Some patients also showed specific responses to the factually incorrect compared to the correct sentences in language areas. EEG studies focused on congruous versus incongruous sentences, evidencing N400 effects in behaviorally unresponsive patients, which would however be less frequent than in conscious brain-injured subjects. Increased N400 peak amplitudes within the fronto-central cortical areas were particularly shown in response to incongruous final words in DoC patients, and a delayed N400 effect was found in UWS compared to MCS patients. Yet, other studies could only objectify a late positive complex. Regarding prognosis, the absence of N400 could predict poorer outcomes as well as subsequent aphasia. Patients with (covert) command-following would finally present a better

functional differentiation between the auditory and frontoparietal networks during narrative listening compared to unresponsive patients.

e. Familiar, musical and/or emotional linguistic stimuli

Numerous studies, most of them using EEG, focused on the cortical activity elicited by the listening of subject's own name (SON), which is an effective auditory stimulus for triggering an involuntary capture of attention (Tateuchi, Itoh, & Nakada, 2015). The SON is also known to be processed distinctively from other sounds. As SON may still be considered as a "verbal" stimulus, we decided to add this literature to the present review, for the sake of completeness.

According to Kempny et al. (2018), 4/16 patients (3 MCS and 1 UWS) showed a significant difference in response to SON compared to other names with EEG latencies. Using a comparable paradigm, Sergent et al. (2017) showed a significant P3 in 9/15 healthy subjects, 4/8 MCS patients, 1/4 UWS patient, but not in the EMCS patient. Similarly, Perrin et al. (2006) observed a P3 component in response to the SON in 4/4 LIS patients, 6/6 MCS patients and 3/5 UWS patients, and the P3 latency was significantly delayed for MCS and UWS patients compared to healthy subjects. By adding the command "listen carefully for pitch change", Schnakers et al. (2015) observed an enhanced P3 amplitude in 9/26 DoC patients (5 MCS+, 3 MCS- and 1 UWS). Compared to control subjects, patients' response was widely distributed over frontoparietal areas and not present in all blocks. More recently, Crivelli et al. (2019) found, in a group of 21 UWS patients, increased skin conductance, heart rate measures and alpha activity (over frontal areas) in response to SON compared to other names. Nevertheless, Lechinger et al. (2016) failed to show such stimulus-specific processing, even if general reactivity toward any auditory input allowed for differentiation between UWS and MCS.

Besides, Laureys et al. (2004) used $H_2{}^{15}O$-PET and compared passive listening of frequency-modulated noise, infant cries and SON. Auditory stimuli with

emotional valence (infant cries and SON) compared to the noise induced a more widespread activation (i.e., bilateral inferior parietal lobules including angular gyrus, right temporoparietal junction area, left dorsal prefrontal regions and Broca area, precuneal and anterior cingulate/mesiofrontal cortices). Additionally, an fMRI single-case study showed higher brain activity during hearing SON than other names in the bilateral medial prefrontal cortex, and to a lesser significance (uncorrected $p < 0.005$) in the left temporo-parietal and superior frontal cortex (Staffen et al., 2006).

Li et al. (2018) recently compared passive listening of SON or music, as well as habit stimulation (i.e., alcohol for alcoholic patients or cigarette smell for smoking patients). The highest degree of EEG responses was found in the SON stimulation, followed by habit and music. EEG wavelet energy and response coefficient were found to be different both between habit and music stimulation, and between habit and SON stimulation. Regarding music stimulation, Wu et al. (2011) used EEG along with commonly used words and popular songs as auditory stimuli in UWS patients, MCS patients and healthy subjects. They identified lower EEG response (i.e., non-linear indices) in patients compared to controls, and the lowest was shown in UWS patients.

Importantly, Edlow et al. (2017) proposed language- and music-based tasks in patients with and without behavioral evidence of language function. Using fMRI, 9/16 patients showed response to language stimuli within Heschl's gyrus and superior temporal gyrus, whereas 8/15 patients showed such response to music stimuli. Using EEG, 9/14 patients showed response to language stimuli (e.g., spectral power changes with decrement in delta power and more pronounced change in the left temporal area), whereas 8/13 showed response to music stimuli. Note that this study may particularly be considered of high quality as all methodological aspects (except the use of a convenience sample) presented a low risk of bias.

One last research from Kotchoubey et al. (2009) investigated the recognition of affective prosody in DoC (and LIS), who were asked to listen to emotional vocalizations (exclamations of joy such as "heey!" versus exclamations of woe: "oooh!" deviant). Significant differences between emotionally positive and negative

stimuli were found in 6/27 DoC patients, but no difference was found between UWS and MCS patients.

Overall, EEG responses to SON might differ from responses to other names, and P3 components elicited by SON in healthy conscious subjects can also occur in DoC patients (even if less systematic or with delay). Neuroimaging studies particularly highlighted the role of left temporo-parietal cortex in detection of SON. This specific stimulus was found with the highest degree of EEG responses compared to habit and music. Similarly to speech listening, music further allowed to identify a substantial proportion of patients with fMRI and EEG higher-order cortical responses. Patients' responses following SON and music listening should however not be interpreted as 'residual language abilities' *per se* since they do not only involve verbal material. Finally, residual affective prosody capacities were shown in several UWS and MCS patients.

These studies provided evidence of residual speech processing in an important proportion of DoC patients, by showing cortical activation in response to verbal stimuli, similarly to conscious subjects. Specifically, the temporal lobules (i.e., middle and superior temporal gyri) were shown to be activated in response to speech using fMRI in several patients, as well as the left angular gyrus and left inferior frontal gyrus. The literature also reported more negative ERPs to speech than those elicited by noises, as well as N400 or less complex processes regarding fronto-centro-parietal areas, which could be related to residual semantic processing in DoC patients. With regard to the quality assessment, all of them present high risk of bias regarding the examined population as they included single cases or convenience samples, and most of them also remained unclear on several methodological aspects (i.e., blinding processes and interval between behavioral assessments and measurement of residual speech processing). Nevertheless, low concerns were reported regarding the applicability of patient selection, index test and reference standard.

Table 1. Residual language abilities in DoC patients		
Outcomes	**Main results**	**Quality**
1) Behavioral language assessment	CAVE for detection of visual recognition abilities, but need for other tools	High risk of bias
2) Language-related signs of consciousness	MCS+ > MCS-: - Glucose metabolism of left-sided cortical areas including language areas - Central gamma and posterior alpha power, complexity measures - Potentially, grey matter volume in left language areas - Thalamo-premotor and thalamo-temporal connectivity	High risk of bias at least for population and index test (neuroimaging or EEG) as there was no blinding regarding patients' diagnosis
3) Detection of command-following by means of brain-computer interfaces	- Motor imagery, counting and visual recognition tasks with verbal commands - 15% of UWS patients with cognitive-motor dissociation (Kondziella et al., 2016) - fMRI more sensitive but less specific than EEG	High risk of bias regarding the population, unclear on several methodological aspects (e.g., blinding)
4) Measure of cortical activity in response to language stimulation	As in conscious subjects, possible differential cortical response to speech vs. noise, intelligible vs. less intelligible speech, semantically related vs. unrelated words, semantically unambiguous or congruous vs. ambiguous or uncongruous sentences - fMRI: temporal lobules (middle and superior temporal gyri), left angular and inferior frontal gyri - EEG: N400 effects in fronto-centro-parietal areas	High risk of bias regarding the population, unclear on several methodological aspects (e.g., blinding)

8. Objectives

The results of our systematic review are summarized in table 1. Accordingly, the use of brain-computer interfaces (EEG, fMRI or other devices) is already widely documented. Command-following ability was revealed in a reduced but still important proportion of DoC patients. Such devices might allow communicating with a few behaviorally unresponsive patients. The presence of residual language processing in response to speech stimulations was also highlighted in numerous studies by means of EEG and/or neuroimaging. Importantly, some DoC patients were reported with the ability to detect: speech compared noise, intelligible speech compared to less intelligible speech (including backwards speech), words' lexical effect and semantic relatedness, sentence incongruence and ambiguity, narratives as well as familiar, musical and/or emotional linguistic stimuli. The presence of cognitive-motor or higher-order cortex motor dissociations might also lead to better outcomes.

The neural correlates of the language-related signs of consciousness were addressed in previous literature. In the study of Bruno et al. (2012) using FDG-PET, MCS+ patients showed higher glucose metabolism than MCS- patients in a left fronto-temporo-parietal network. This study however included a reduced sample of 27 MCS patients. Only potential differences of grey matter impairment in both MCS subcategories were also reported (Guldenmund et al., 2016). In our **Study 1,** we therefore aimed to replicate FDG-PET analyses in a larger sample of patients, in parallel with structural analyses of grey matter volume in both subcategories. In line with the previous studies, MCS+ patients would exhibit higher glucose metabolism and less grey matter atrophy compared to MCS- patients, in particular in language-related areas. We also focused on regions known to be involved in conscious processes, such as the thalamus and precuneus (e.g., Vanhaudenhuyse et al., 2011). The MCS could indeed be sub-categorized on the basis of both consciousness level

and language impairment. Given the implication of brain metabolic function in the sub-categorization of MCS patients (Bruno et al., 2012), we further aimed to explore brain functional connectivity by means of resting state fMRI in our **Study 2**. We investigated this language-related left frontoparietal network along with the auditory network, the right frontoparietal network (involved in perception of surroundings; Laird et al., 2011) as well as consciousness-related networks: the default mode network (DMN; including anticorrelations) and thalamo-cortical network. Measurements of brain structure and left-right hemispheric differences were finally controlled to ensure robust data. We hypothesized that the clinical sub-categorization of MCS would be supported by differences regarding the language-related left frontoparietal network, whereas brain structure and function in the other networks would be similar in both subcategories. Finally, the clinical relevance of these studies led us to consider the longitudinal recovery of language-related signs of consciousness. Our database included three patients that were examined at two time points: once with the behavioral diagnosis of MCS- and then MCS+. In our **Study 3**, we consequently investigated the neural correlates of the recovery of command-following (the most frequent language-related sign of consciousness), at the individual level. More preserved brain glucose metabolism and structure was expected at time 2 (i.e., MCS+) compared to time 1 (i.e., MCS-) in language areas.

Our review only presented a few attempts of language behavioral assessments in various studies with high concern regarding the included population and other various quality criteria. The feasibility of some of these assessments in DoC patients was questioned. The Cognitive Assessment by Visual Election (CAVE) (Murphy, 2018) was however presented as a reliable tool, which is based on the ability to understand language and visually fixate objects. Our **Study 4** therefore aimed to use the CAVE along with CRS-R and neuroimaging assessments (i.e., FDG-PET and VBM) in patients in MCS and EMCS, and thus examine their behavioral, cognitive and cerebral data. We hypothesized an association between patients' structural and functional brain damage and their behavioral/cognitive profile, which would be consistent with previous studies establishing neural correlates of behavior, language

and cognition. The CAVE does however not distinguish various language domains nor include items controlling for psycholinguistic effects (e.g., word length or frequency), and more information would be needed for speech therapists to refine patients' language profile. We consequently presented the development and validation of the "Brief Evaluation of Receptive Aphasia" (BERA) in our **Study 5**, which specifically assesses phonological, semantic and morphosyntactic receptive abilities. BERA assessments were performed in healthy subjects (with an expected ceiling effect), in aphasic conscious patients (to determine intra- and inter-rater reliability, internal and concurrent validity), and in post-comatose DoC patients along with repeated CRS-R, FDG-PET and VBM. The presence of language impairment is expected to be documented by combining the BERA and CRS-R assessments with measurement of brain glucose metabolism and grey matter structure.

In sum, this thesis mainly aims at exploring the recovery of language residual abilities in post-comatose patients, (I) by further investigating the neural correlates of language-related signs of consciousness as detected using the CRS-R, and thus comparing MCS- and MCS+ patients, and (II) by intending to measure residual language functions using new behavioral bedside assessment tools combined to neuroimaging.

Experimental part I. Neural correlates of minimally conscious state *minus* versus *plus*

Communication is one of the most important aspects in the recovery of DoC patients because it allows them to interact with their environment and to express their needs. Regaining command-following, intelligible verbalization and/or intentional communication appears to be the first step before implementing functional "yes/no" communication codes, and is therefore crucial. In this first part, we aim to further explore the neural correlates of these language-related signs of consciousness, by means of FDG-PET, VBM and fMRI.

Based on the following publications:

Aubinet C, Cassol H, Gosseries O, Bahri MA, Larroque SK, Majerus S, Martial C, Martens G, Carrière M, Chatelle C, Laureys S, & Thibaut A (2020). Brain metabolism but not grey matter volume underlies the presence of language function in the minimally conscious state. *Neurorehabilitation and Neural Repair, 34*(2), 172-184.

Aubinet C, Heine L, Martial C, Larroque S, Majerus S, Laureys S, Di Perri C (2018). Clinical subcategorization of minimally conscious state according to resting functional connectivity. *Human Brain Mapping, 39*(11), 4519-4532.

Aubinet C, Panda R, Larroque SK, Cassol H, Bahri MA, Carrière M, Wannez S, Majerus S, Laureys S, Thibaut A (2019). Reappearance of command-following is associated with the recovery of language and internal-awareness networks: A longitudinal multiple-case report. *Frontiers in Systems Neuroscience, 13*(8), 1-6.

Study 1. Brain metabolism and grey matter volume in minimally conscious state *minus* versus *plus*

The minimally conscious state (MCS) is subcategorized into MCS- and MCS+, depending on the absence or presence of high-level behavioral responses such as command-following. We aim to investigate the functional and structural neuroanatomy underlying the presence of these responses in MCS- and MCS+ patients. In this cross-sectional retrospective study, chronic MCS patients were diagnosed using repeated Coma Recovery Scale-Revised assessments. Fluorodeoxyglucose-positron emission tomography data were acquired on 57 patients (16 MCS- and 41 MCS+) and MRI with voxel-based morphometry analysis was performed on 66 patients (17 MCS- and 49 MCS+). Brain glucose metabolism and grey matter integrity were compared between patient groups and control groups. A metabolic functional connectivity analysis testing the hypothesis of preserved language network in MCS+ compared to MCS- was also done. Patients in MCS+ presented higher metabolism mainly in the left middle temporal cortex, known to be important for semantic processing, compared to the MCS- group. The left angular gyrus was also functionally disconnected from the left prefrontal cortex in MCS- compared to MCS+. No significant differences were found in grey matter volume between patient groups. The clinical sub-categorization of MCS is supported by differences in brain metabolism but not in grey matter structure, suggesting that brain function in the language network is the main support for recovery of command-following, intelligible verbalization and/or intentional communication in the MCS. Better characterizing the neural correlates of residual cognitive abilities of MCS patients contributes to reduce their misdiagnosis and to adapt therapeutic approaches.

1. Aim and hypotheses

Bruno et al. (2012) previously showed higher brain glucose metabolism in a left fronto-temporo-parietal network in patients in minimally conscious state *plus* (MCS+; with preserved language-related signs of consciousness) compared to patients in minimally conscious state *minus* (MCS-). They did however only include 27 patients and grey matter volume differences in both MCS subcategories were not investigated. We therefore considered that their analyses should be replicated in a larger sample of patients and paralleled with structural analyses of grey matter volume. This first study consequently followed these two objectives.

Specifically, we aim to examine the regional and global brain metabolism and the metabolic functional connectivity differences in patients in MCS- versus MCS+ by means of fluorodeoxyglucose-positron emission tomography (FDG-PET), as well as structural differences between these subcategories by means of grey matter volume atrophy quantification (i.e., voxel-based morphometry; VBM). In line with previous studies (Bruno et al., 2012; Guldenmund et al., 2016), we expect that MCS+ patients exhibit higher glucose metabolism and less grey matter atrophy compared to MCS- patients, in particular in language-related areas.

2. Methods

a. Participants

Behavioral and neuroimaging data were collected during a one-week hospitalization of patients with disorders of consciousness (DoC), for diagnostic and prognostic purposes. The FDG-PET and magnetic resonance imaging (MRI) acquisitions were performed within four days and patients were assessed by a team

of experienced clinician-researchers using the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004; Schnakers et al., 2008).

At least five CRS-R assessments were performed for each patient (including on the days of neuroimaging assessments) in a short time period (i.e., 10 days maximum) and the best diagnosis of MCS was retained (Wannez, Heine et al., 2017). Patients were categorized as being MCS- (criteria: presence of object localization, visual pursuit and fixation, automatic motor reaction, object manipulation and/or localization to noxious stimulation) or MCS+ (criteria: presence of consistent/reproducible movement to command including object recognition, intelligible verbalization and/or intentional communication) (Bruno et al., 2011; Giacino et al., 2002; Giacino et al., 2004).

Exclusion criteria were: (a) premorbid neurological conditions, (b) time post-injury less than 28 days, (c) age lower than 18 years old, (d) diabetes, (e) MRI contra-indication (e.g., pacemaker), and masking/segmentation issues (e.g., structural brain damage exceeding 25% of the whole brain volume disabling reliable spatial normalization to the standardized stereotaxic brain template) (figure 3). None of the patients who participated in the previous FDG-PET study of Bruno et al. (2012) was included in the present research. Nevertheless, one patient from our case series (Aubinet et al., 2019) and nine patients who participated in our MRI study (Aubinet, Larroque et al., 2018) were included in these VBM analyses (10/66 patients).

Two samples of healthy control subjects (HCS; *n* total = 58) were recruited using advertisements posted at the university and none had a history of psychiatric or neurological disease. They were composed of 34 participants (age range 19-70 years old, 15 women) for FDG-PET imaging and 36 participants (age range 20-75 years old, 13 women) for VBM imaging.

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège (n° 2009-241). Written informed consent to participate in the study was obtained from all HCS and from the legal surrogates of the MCS patients.

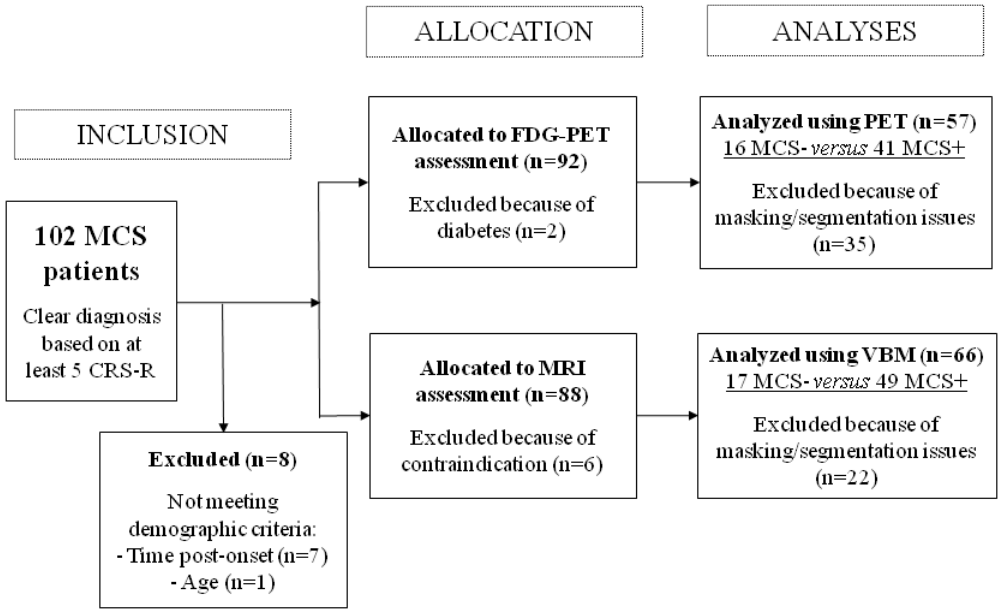

Figure 3. *Selection of patients according to exclusion criteria.. MCS: minimally conscious state; FDG-PET: fluorodeoxyglucose-positron emission tomography; MRI: magnetic resonance imaging; VBM: voxel-based morphometry.*

b. FDG-PET

We acquired FDG-PET data with a Gemini TF CT scanner (Philips Medical Systems). Following intravenous injection of 150 to 300 MBq FDG, we recorded a single PET frame for 12 minutes, after circulation of the tracer for at least 30 minutes. We kept the patients awake during the uptake period. The images were corrected for attenuation using X-ray computed tomography, as well as for random, scatter events and physical decay. All data were preprocessed as described elsewhere (Phillips et al., 2011), smoothed with an isotropic 14 mm full-width at half-maximum (FWHM) Gaussian kernel and analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK). To partially overcome the issue of brain lesions, the normalization was performed using a customized FDG template resulting from the average of images of DoC patients and healthy control subjects (separated data set), as it was presented in the

previous study of Phillips et al. (2011). A global normalization was performed by proportional scaling.

We used the FDG-PET Standardized Uptake Values (SUV) to estimate the global cerebral metabolic rate of glucose consumption: $SUV = \frac{(Decay\ corrected\ Voxel\ Intensity)}{\frac{Injected\ Dose}{Body\ Weight}}$ at the single subject level. For regional brain metabolism, the design matrices included the scans of both patient groups and the scans of the HCS. In a first analysis, brain regions with significantly decreased metabolism were identified in MCS- and MCS+ patients compared to HCS (i.e., MCS- versus HCS and MCS+ versus HCS). We also investigated the direct comparison between patient groups (i.e., MCS- versus MCS+). In a second analysis, we used a seed-based approach to explore which brain regions' metabolism correlates with the areas that most differentiate MCS- from MCS+. In this metabolic connectivity analysis, the design matrix included the same data as in the first analysis and tested the group differences in mean levels of glucose consumption. We looked for cortical regions that presented a significant difference in reciprocal modulation with areas found to be more preserved in MCS+ compared to patients in MCS- (i.e., MCS- versus MCS+ in the first analysis).

Two supplementary analyses were also performed. First, the initial MCS+ sample was reduced to 20 MCS+ patients (i.e., randomly chosen and matched to the MCS- group for gender, age, etiology and time post-injury) to ensure that the FDG-PET results were not driven by the larger sample size of the MCS+. Moreover, the 7 MCS- patients who had both FDG-PET and MRI data were compared to 7 MCS+ patients matched for gender, age, etiology and time post-injury, using both FDG-PET and VBM analyses.

c. VBM

Structural MRI data were obtained with T1-weighted 3D gradient echo sequence (120 slices, repetition time 2300 ms, echo time 2.47 ms, voxel size 1 x 1 x

1.2 mm^3, flip angle 9°, field of view 256 x 256 mm^2). A T1 VBM analysis (Ashburner & Friston, 2000) was carried out with VBM8 toolbox (http://www.neuro.uni-jena.de/vbm/), with non-linear warping and modulation of the grey matter to ensure the preservation of the volumes after the normalization step. The images were segmented into grey and white matter and cerebrospinal fluid using the unified segmentation module. These segmented grey and white matter images were then used to obtain a more accurate inter-subject registration model using DARTEL (Ashburner, 2007). This model alternates between computing a group template and warping the individual's tissue probability maps in alignment with this template and ultimately creates the individual flow field of each participant. We then normalized the images of each participant into the MNI space using the obtained individual flow field and a study template (obtained on a separate set of data from DoC and healthy subjects). Normalized modulated grey matter data were smoothed with an isotropic Gaussian kernel of 12 mm FWHM. A full factorial design matrix was constructed, including the scans of both patient groups and the scans of the MRI-specific HCS, with the age of subjects centered to the mean as a regressed covariate. Indeed, grey matter structure was shown to be particularly dependent on age (Minkova et al., 2017).

d. Statistical analyses

We first checked the potential equivalence between patient groups regarding the time post-injury, age and CRS-R total score using Wilcoxon tests, and the gender and etiology (traumatic versus non-traumatic) using Chi-squared tests. The same statistical analyses were performed to investigate the equivalence of age and gender between the patient groups and their corresponding control group.

Regarding global brain metabolism, Wilcoxon tests were performed to check for SUV differences between patient groups. FDG-PET analyses for regional brain metabolism were based on t-tests and identified: (a) brain areas showing hypometabolism in patient groups as compared to HCS; (b) brain areas showing

significant differences in the direct comparison of both patient groups (MCS- < MCS+); (c) brain areas whose glucose consumption significantly correlates with that of regions emerging in the previous analysis. VBM analyses, also based on t-tests, intended to identify: (a) brain areas showing grey matter impairment in patient groups as compared to HCS; and (b) brain areas showing significant differences by directly comparing both patient groups (MCS- < MCS+). All FDG-PET and VBM results were thresholded at $p < 0.05$ with family wise error (FWE) correction for whole brain multiple comparisons. Furthermore, to compare with previous studies that used a false discovery rate (FDR) correction (Bruno et al., 2012), results are also given at $p < 0.05$ FDR corrected. FWE correction is more conservative but less sensitive (i.e., avoid false-positives), whereas FDR correction is more sensitive but less specific (i.e., avoid false-negatives) (Chumbley et al., 2010).

3. Results

a. Participants

Between January 2011 and June 2018, 102 severely brain-injured patients stayed for one week in our hospital and were diagnosed MCS as assessed by repeated CRS-R. Following the exclusion criteria (figure 3), FDG-PET analyses focused on 16 MCS- (4 women, aged 42 ± 18 years) and 41 MCS+ (19 women, aged 39 ± 16 years) patients. VBM analyses were conducted on 17 MCS- (9 women, aged 38 ± 14 years) and 49 MCS+ (18 women, aged 43 ± 17 years) patients.

As shown in table 2, 36 patients (7 MCS- and 29 MCS+) were included in both FDG-PET and VBM analyses. Individual demographic data of patients and their diagnosis criteria of MCS- or MCS+ are also reported in this table. All MCS+ patients exhibited reproducible command-following in the present research.

Table 2. Individual demographic data of patients

Patients	Group	Age	Gender	Etiology	Time post-injury (days)	MCS criteria	Best CRS-R total score	Analyses	Handed-ness
1	MCS-	24	Male	TBI	167	VP – VF	8	PET	R
2	MCS-	57	Male	NTBI	247	VF	7	PET	R
3	MCS-	74	Male	NTBI	46	OL –VP – VF	10	PET	R
4	MCS-	64	Male	NTBI	400	VP – VF – OM	12	PET	R
5	MCS-	22	Male	TBI	1016	VF – VP	8	PET	R
6	MCS-	49	Male	TBI	224	OM	12	PET	R
7	MCS-	31	Male	NTBI	100	OL – VP – OM	13	PET	R
8	MCS-	60	Male	TBI	2147	OL – VP – VF – OM	13	PET	MD
9	MCS-	21	Female	NTBI	1102	VP – OM	12	PET	R
10	MCS-	25	Male	TBI	322	OM	12	PET-VBM	MD
11	MCS-	28	Male	TBI	517	VP – VF	10	PET-VBM	R
12	MCS-	49	Female	NTBI	467	VF	9	PET-VBM	R
13	MCS-	42	Female	NTBI	222	VP – VF	8	PET-VBM	R
14	MCS-	19	Male	TBI	1306	VP – VF	7	PET-VBM	R
15	MCS-	46	Female	TBI	238	VP – VF	10	PET-VBM	R
16	MCS-	54	Male	NTBI	159	VP – VF – OM	13	PET-VBM	R
17	MCS-	40	Female	TBI	1290	VP – VF	11	VBM	R
18	MCS-	30	Female	TBI	565	VF	12	VBM	L
19	MCS-	53	Female	NTBI	49	VP	7	VBM	R

20	MCS-	30	Male	TBI	39	OM	6	VBM	R
21	MCS-	26	Female	TBI	36	VP – VF – OM	13	VBM	MD
22	MCS-	29	Female	NTBI	745	VF	5	VBM	R
23	MCS-	29	Male	TBI	68	VP – VF	5	VBM	MD
24	MCS-	52	Male	NTBI	1459	OL – VP – VF – OM	13	VBM	R
25	MCS-	68	Female	NTBI	1379	PL	8	VBM	R
26	MCS-	25	Male	TBI	333	VP – VF	10	VBM	R
27	MCS+	19	Female	TBI	485	CF – IC	13	PET	R
28	MCS+	62	Female	NTBI	714	CF	17	PET	R
29	MCS+	30	Female	TBI	565	CF	12	PET	L
30	MCS+	47	Male	TBI	529	CF – IC	13	PET	R
31	MCS+	35	Male	NTBI	532	CF – IC	20	PET	R
32	MCS+	78	Female	TBI	2070	CF – IC	20	PET	R
33	MCS+	50	Female	NTBI	273	CF – IC	13	PET	R
34	MCS+	61	Male	TBI	131	CF	12	PET	L
35	MCS+	27	Male	TBI	220	CF	12	PET	A
36	MCS+	48	Female	TBI	287	CF – IC	11	PET	MD
37	MCS+	67	Male	NTBI	39	CF – IC – IV	15	PET	MD
38	MCS+	49	Female	TBI	477	CF	8	PET	R
39	MCS+	19	Male	TBI	428	CF – IC	11	PET-VBM	R
40	MCS+	27	Male	TBI	1544	CF	12	PET-VBM	R

41	MCS+	32	Female	TBI	557	CF	11	PET-VBM	R
42	MCS+	30	Female	NTBI	2407	CF	10	PET-VBM	MD
43	MCS+	27	Female	TBI	1013	CF	11	PET-VBM	R
44	MCS+	50	Male	TBI	253	CF	21	PET-VBM	R
45	MCS+	32	Female	TBI	573	CF – IC	16	PET-VBM	R
46	MCS+	21	Female	NTBI	620	CF – IC	13	PET-VBM	R
47	MCS+	38	Male	NTBI	202	CF	11	PET-VBM	R
48	MCS+	26	Female	TBI	310	CF	10	PET-VBM	R
49	MCS+	23	Male	TBI	1231	CF	13	PET-VBM	MD
50	MCS+	60	Male	NTBI	711	CF	13	PET-VBM	R
51	MCS+	30	Female	TBI	2729	CF	9	PET-VBM	R
52	MCS+	45	Male	TBI	4786	CF	11	PET-VBM	R
53	MCS+	21	Female	TBI	510	CF	7	PET-VBM	L
54	MCS+	29	Male	NTBI	405	CF	17	PET-VBM	L
55	MCS+	25	Male	TBI	1153	CF	16	PET-VBM	R
56	MCS+	46	Male	NTBI	1379	CF	11	PET-VBM	L
57	MCS+	55	Female	TBI	198	CF	18	PET-VBM	R
58	MCS+	35	Male	TBI	1327	CF	9	PET-VBM	R
59	MCS+	24	Male	TBI	2036	CF – IC	18	PET-VBM	R
60	MCS+	23	Male	TBI	641	CF	12	PET-VBM	MD
61	MCS+	42	Female	NTBI	266	CF	10	PET-VBM	R

62	MCS+	40	Male	TBI	329	CF	16	PET-VBM	R
63	MCS+	43	Female	NTBI	100	CF	6	PET-VBM	R
64	MCS+	22	Male	TBI	425	CF	12	PET-VBM	L
65	MCS+	69	Male	NTBI	312	CF – IC	17	PET-VBM	R
66	MCS+	46	Male	TBI	648	CF	16	PET-VBM	R
67	MCS+	65	Female	NTBI	421	CF	12	PET-VBM	R
68	MCS+	67	Female	NTBI	284	CF	7	VBM	R
69	MCS+	49	Male	TBI	54	CF	14	VBM	MD
70	MCS+	20	Male	TBI	389	CF	15	VBM	R
71	MCS+	54	Male	TBI	2082	CF	15	VBM	R
72	MCS+	43	Female	NTBI	3237	CF	8	VBM	R
73	MCS+	46	Male	NTBI	227	CF	9	VBM	R
74	MCS+	57	Male	NTBI	254	CF	6	VBM	R
75	MCS+	48	Female	NTBI	205	CF	7	VBM	L
76	MCS+	45	Female	NTBI	34	CF – IC – IV	19	VBM	R
77	MCS+	74	Female	NTBI	46	CF	13	VBM	R
78	MCS+	24	Male	TBI	2686	CF	9	VBM	R
79	MCS+	72	Male	NTBI	3063	CF	9	VBM	R
80	MCS+	25	Male	TBI	529	CF	12	VBM	R
81	MCS+	57	Male	NTBI	392	CF	7	VBM	R
82	MCS+	62	Male	NTBI	38	CF	16	VBM	MD

83	MCS+	66	Male	NTBI	318	CF	15	VBM	A
84	MCS+	74	Male	NTBI	98	CF	9	VBM	R
85	MCS+	67	Male	TBI	28	CF	14	VBM	R
86	MCS+	39	Male	NTBI	254	CF – IC	17	VBM	R
87	MCS+	54	Female	NTBI	389	CF	11	VBM	R

MCS : minimally conscious state ; TBI : traumatic brain injury ; NTBI : non-traumatic brain injury ; VP: visual pursuit; VF: visual fixation; OL: object localization; OM: oriented movements; CF : command-following ; IV : intelligible verbalization ; PL: pain localization; IC : intentional communication; PET: positron emission tomography; VBM: voxel-based morphometry; R: right; L: left; MD: missing data; A: ambidextrous.

Table 3. Comparison of patient groups according to demographic data				
FDG-PET	**MCS- (*n* = 16)**	**MCS+ (*n* = 41)**		
Age	41.57 ± 17.57 [a]	39.48 ± 15.77	W [b] = 345	p = 0.772
Time post-injury (days)	542.5 ± 570.64	825.27 ± 901.39	W = 227.5	p = 0.076
CRS-R total score	10.25 ± 2.21	13.05 ± 3.55	W = 183	p = 0.01*
Gender	4 female	19 female	χ^2 [c] = 2.178	p = 0.14
Etiology	8 TBI	27 TBI	χ^2 = 1.22	p = 0.27
Handedness	0 L/14 R (2 MD)	6 L/29 R (6 MD)	χ^2 = 2.735	p = 0.098
VBM	**MCS- (*n* = 17)**	**MCS+ (*n* = 49)**		
Age	37.9 ± 13.65	42.66 ± 16.81	W = 361	p = 0.424
Time post-injury (days)	540.76 ± 508.76	859.61 ± 1024.91	W = 356.5	p = 0.383
CRS-R total score	9.41 ± 2.72	12.22 ± 3.69	W = 242.5	p = 0.011*
Gender	9 female	18 female	χ^2 = 1.371	p = 0.242
Etiology	10 TBI	25 TBI	χ^2 = 0.309	p = 0.579
Handedness	1 L/13 R (3 MD)	5 L/38 R (6 MD)	χ^2 = 0.226	p = 0.635

*[a] Expressed as mean ± standard deviation; [b] Wilcoxon rank-sum test; [c] Chi-squared test; * p<0.05; MCS : minimally conscious state ; FDG-PET: fluorodeoxyglucose-positron emission tomography; VBM: voxel-based morphometry; TBI: traumatic brain injury; NTBI: non-traumatic brain injury; L: left-handed; R: right-handed; MD: missing data*

Age and time post-injury did not differ between patient groups (table 3), neither did gender, etiology and handedness. As expected, CRS-R total scores differed between groups with higher scores for MCS+ patients. Regarding FDG-PET data, there was no significant difference between patients and HCS for age (W = 1069; p = 0.284) and gender (χ^2 = 0.037; p = 0.847). There was also no significant difference between patients and HCS for the VBM analyses (age: W = 1405; p = 0.13; gender: χ^2 = 0.225; p = 0.635).

b. FDG-PET analyses

Regarding global brain glucose metabolism, MCS+ patients showed a significantly higher SUV mean (median = 4.51) as compared to MCS- patients (median = 3.47; W = 161, p = 0.014). Regional brain metabolism results are presented in figure 4 and appendix II (supplementary table 1).

Comparison between patient groups and healthy subjects

Compared to HCS, the group of MCS- patients presented an extended hypometabolism in bilateral frontal and temporo-parietal areas including the left angular gyrus (BA39) and middle temporal gyrus (BA21), as well as left caudate and left thalamus (figure 4A – on the left). Compared to HCS, the group of MCS+ patients showed hypometabolism in bilateral frontal lobules including middle frontal gyri (BA10), left anterior cingulate cortex (BA32), and left thalamus (figure 4A – on the right).

Comparison between patient groups

Compared to the MCS- group, MCS+ patients exhibited higher metabolism in the left middle temporal cortex (BA21). The FDR-corrected results also showed higher metabolism in MCS+ patients in the left angular gyrus (BA39), left middle frontal gyrus (BA9), left inferior frontal gyrus (*pars opercularis*; BA44), bilateral prefrontal cortex/supplementary motor area (BA8) and premotor cortex (BA6), compared to MCS- patients. These results are shown in figure 4B and table 4.

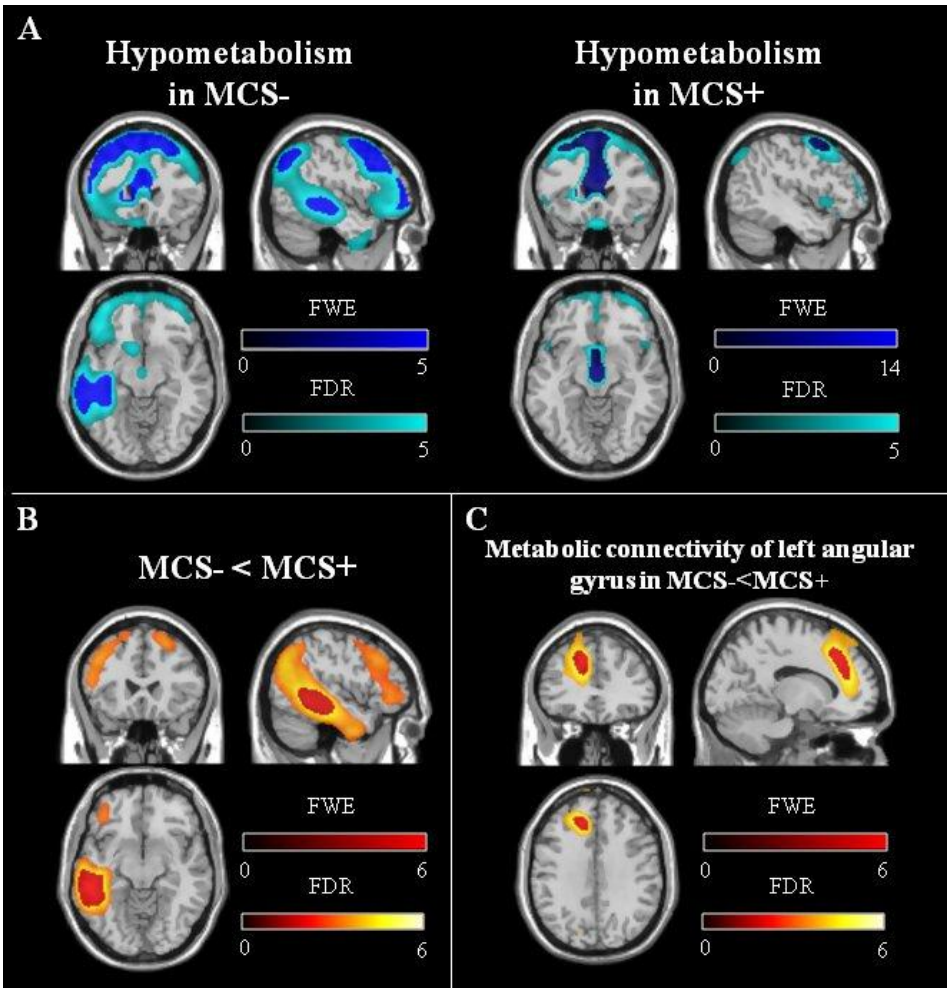

Figure 4. *Brain metabolism results using positron emission tomography. MCS: minimally conscious state; FWE: family-wise error; FDR: false discovery rate. 4A: Comparison of glucose uptake between patients in MCS- and healthy subjects, and between patients in MCS+ and healthy subjects; 4B: Comparison of glucose uptake between patients in MCS- and MCS+; 4C: Comparison of metabolic connectivity of the left angular gyrus between patients in MCS- and MCS+. All color scales correspond to the t-test value.*

The supplementary analysis performed with a smaller sample of MCS+ patients (i.e., 16 MCS- versus 20 MCS+) showed that these patients had higher metabolism than MCS- patients in the left middle temporal cortex (BA21), left fusiform cortex (BA37), left inferior and middle frontal gyrus (BA44 and BA9), left prefrontal cortex/supplementary motor area (BA8), as well as left inferior frontal gyrus (BA47) (FWE correction). Similar results (notably concerning the left middle temporal cortex) were obtained when comparing 7 MCS- and 7 MCS+ patients, with

uncorrected $p < 0.001$ (but not using FDR or FWE corrections). These data are presented in appendix II (supplementary analyses 1 and 2). As the differences between patient groups regarding time post-injury and handedness were close to significant, we also performed supplementary FDG-PET analyses: (i) including time post-injury as covariate (appendix II – supplementary analysis 3), and (ii) excluding patients with left-handedness, ambidexterity or missing handedness data (appendix II – supplementary analysis 4). Both analyses also led to similar results.

Table 4. Brain glucose metabolism results

	Brain region	***x***	***y***	***z***	***Z* value**	***p* value***
MCS- < MCS+	Left middle temporal gyrus (BA21)**	-54	-38	-8	5.323	<0.001
	Left angular gyrus (BA39)	-46	-70	28	3.699	<0.001
	Left middle frontal gyrus (BA9)	-44	26	36	3.318	<0.001
	Left prefrontal cortex/supplementary motor area (BA8)	-36	22	46	3.218	0.001
	Left inferior frontal gyrus (*pars opercularis*; BA44)	-52	20	18	3.195	0.001
	Right premotor cortex (BA6)	20	8	68	3.273	0.001
	Right prefrontal cortex/supplementary motor area (BA8)	24	24	54	3.135	0.001
	Left premotor cortex (BA6)	-18	10	68	3.027	0.001
Connectivity of left angular gyrus in MCS- < MCS+	Left prefrontal cortex/supplementary motor area (BA8)**	-12	30	40	5.125	<0.001
	Left inferior occipital gyrus (BA19)	-18	-78	32	3.250	0.001

**FDR corrected; ** Areas emerging using the FWE correction; MCS: minimally conscious state.*

Functional connectivity analysis

We then focused on the regions that most differentiated MCS+ from MCS- (i.e., clusters emerging from the previous first [whole sample] comparison between patient groups), and examined their connectivity in the group of MCS+ patients compared to MCS- patients. Among these seeds, the left angular gyrus (BA39; MNI coordinates: $x = -46$, $y = -60$, $z = 33$) was the only one to show significant results. This region presented higher metabolic functional connectivity in MCS+ compared

to MCS- with the left prefrontal cortex/supplementary motor area (BA8) using FWE correction (see figure 4C and table 4).

Individual results

As described in appendix II (supplementary table 2), left frontoparietal hypometabolism was reported in 69% of the MCS- patients (i.e., 11/16), while only 24% of the MCS+ patients had such brain metabolism impairment (i.e., 10/41).

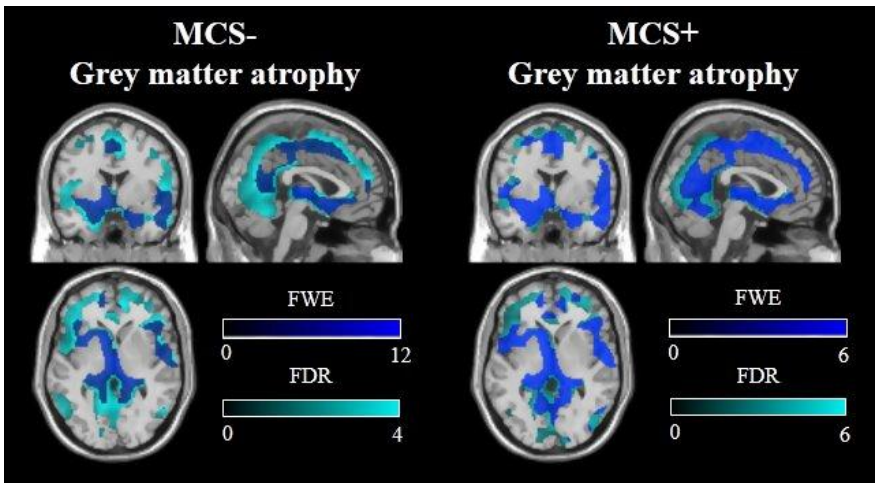

Figure 5. *Brain structure results using voxel-based morphometry. MCS: minimally conscious state; FWE: family-wise error; FDR: false discovery rate. Comparison of grey matter structure volume between patients in MCS- and healthy subjects and between patients in MCS+ and healthy subjects. The color scales correspond to the t-test value.*

c. VBM analyses

The results are presented in figure 5 and appendix II (supplementary table 3). Compared to HCS, the group of MCS- patients exhibited atrophy mainly in the bilateral thalami and angular gyri (BA39), left caudate and insula, left primary sensory area, right orbitofrontal cortex (BA11), right fusiform (BA37) and occipital cortex (BA18). Compared to HCS, the group of MCS+ patients showed atrophy in the bilateral thalami, left caudate, right orbitofrontal cortex (BA11), left insula, left prefrontal cortex (BA8), right orbitofrontal cortex (BA11), right fusiform (BA37)

and occipital cortex (BA18). There was no significant difference in grey matter volume between the groups of patients in MCS- and MCS+.

The supplementary analysis of 7 MCS- and 7 matched MCS+ patients did not lead to significant differences in grey matter volume, neither at a threshold for the *p* value of 0.001 uncorrected, as it was in the whole sample.

4. Discussion

In this study, we aimed to investigate brain function and structure underpinning the recovery of language-related abilities in MCS patients using FDG-PET and VBM techniques by comparing patients with (i.e., MCS+) and without (i.e., MCS-) such behaviors. To our knowledge, this is the first study that examines both brain metabolism and grey matter atrophy in the two groups of MCS patients (MCS- and MCS+). Our main findings show metabolic differences in the left-sided language network sustaining the clinical sub-categorization of the MCS, while no grey matter volume differences were found.

As expected, both patient groups showed decreased cerebral metabolism and structural damage compared to healthy subjects. As in previous studies, we observed an alteration of brain function, in particular in the frontoparietal network (e.g., Aubinet, Larroque et al., 2018; Crone et al., 2014). Moreover, our structural analyses show a significant atrophy for both patient groups in subcortical structures such as the thalamus, which was also previously found to be damaged in MCS patients (Annen et al., 2018; Morozova et al., 2018).

In comparison with the group of MCS- patients, MCS+ patients presented higher metabolism preservation in different language-related areas. Using a more conservative correction (i.e., FWE), higher metabolism was identified in MCS+ compared to MCS- in the left middle temporal cortex, which has been associated to

selective processing of speech (Giraud et al., 2004; Vorobyev et al., 2004), semantic processing (Chou et al., 2006; McDermott et al., 2003) and word generation (Friedman et al., 1998). The FDR correction analysis also highlighted other language-related brain regions: the left angular gyrus (Binder et al., 2009; Dronkers et al., 2004; Humphries et al., 2007), the left middle frontal gyrus (Desmond et al., 1998; Hugdahl et al., 1999; Ranganath, Johnson, & D'Esposito, 2003; Slotnick & Moo, 2006; Zhang, Leung, & Johnson, 2003), the left inferior frontal gyrus (*pars opercularis*) (Anderlini, Wallis, & Marinovic, 2019; Grossman et al., 2002; Heim, Eickhoff, & Amunts, 2008), the prefrontal and premotor cortex as well as supplementary motor area (Fox et al., 2000), which are also involved in various motor functions (Matsumura et al., 2004). These results are in line with previous research showing that the left middle temporal cortex and left angular gyrus could differentiate MCS subcategories at the subject-level (Aubinet et al., 2019), and that a preserved metabolism in these regions was associated with residual language comprehension in three post-comatose patients (Aubinet, Murphy, et al., 2018). The involvement of motor regions is also not surprising since command-following, the most frequent MCS+ criteria to be observed (see table 2), requires both language comprehension and motor execution. Note that the difference in sample size cannot be considered as a confounding factor since we obtained similar results using smaller samples of MCS+ patients (appendix II – supplementary analyses 1 and 2).

Altogether, these findings corroborate previous results reported in the study of Bruno et al. (2012) on a larger sample size (n = 57). In addition, more stringent diagnostic criteria were used following the recent recommendation (i.e., minimum of five CRS-R assessments needed before any diagnosis) (Wannez, Heine, et al., 2017) and therefore are likely to be more accurate than in the Bruno et al.'s study. Finally, FDG-PET analyses here were performed using the computed tomography of each individual patient, which allows a more precise image reconstruction than when the standard ellipse is used (Phillips et al., 2011).

Moreover, the functional connectivity analysis showed a disconnection between the left angular gyrus and the left prefrontal cortex/supplementary motor

area in MCS- as compared to MCS+ (FWE correction), which could reflect a deficit in language integration in MCS- patients. Indeed, several studies have shown a reduced functional connectivity of the left frontoparietal network in aphasic conscious post-stroke patients, which subsequently increased when patients recovered language comprehension (Sharp et al., 2010; Zhu et al., 2014). Additionally, when looking at patients' individual FDG-PET reports, left frontoparietal hypometabolism was reported in 69% of the MCS- patients against 24% of the MCS+ patients, showing the overall difference between the two subgroups. However, it also means that our results are not systematically observable at the subject-level.

The main novelty of this study is to combine functional and structural analyses in MCS- and MCS+ patients at group-level in a representative sample. While functional measurements provide an accurate picture of the functioning brain areas and networks, structural data give information on the location of tissue's damage (Stender et al., 2015). We did not find any grey matter volume difference between MCS- and MCS+. These results suggest that brain function (rather than grey matter structure) is determinant for the presence of clinical signs of language processes in the MCS. The extent and severity of structural lesions are also not predictive of a good outcome as was shown recently (Brown et al., 2019). Grey matter structure as measured with T1, however, was found to discriminate levels of consciousness (i.e., unresponsive wakefulness syndrome versus MCS) with a sensitivity of 0.92 (Annen, Frasso, et al., 2018).

Our work presents several limitations, notably since it is a cross-sectional retrospective study. Moreover, the fact that we did not find grey matter volume differences between both patient groups does not mean that such differences do not exist. Still a recent study using DTI demonstrated a reduced connectivity of premotor and left temporal cortices with the thalamus in MCS- compared to MCS+ patients (Zheng et al., 2017). White matter differences between groups of MCS- and MCS+ should further be investigated. Outcome measurements were also not included in the present study. In this respect, we hypothesize that MCS+ patients

would have a better outcome than MCS- patients given their abilities to interact with their environment and because of smaller neurophysiological impairment. Note that it has recently been shown that MCS- patients have a higher degree of disability at discharged from rehabilitation compared to MCS+ patients (Thibaut, Bodien et al., 2019). Finally, we found a metabolic disconnection within the left frontoparietal network in MCS- compared to MCS+, but further studies should bring evidence on the causality of this disconnection (i.e., missing top-down/bottom up and feedforward/feedback connections).

In conclusion, we aimed to investigate the metabolic activity and functional connectivity needed for residual language abilities in post-comatose patients by means of FDG-PET, as well as possible structural differences between MCS- and MCS+ using VBM. We found metabolic differences sustaining the clinical sub-categorization of MCS. Indeed, MCS+ patients showed preserved glucose metabolism in left-sided language-related areas such as the left middle temporal gyrus, compared to MCS- patients, as well as preserved connectivity in the left frontoparietal network. No grey matter volume differences were identified between MCS- patients and MCS+ patients, suggesting that brain metabolism, more than structural damage, is determinant for the recovery of language-related abilities in the MCS. Our results are of clinical relevance since they contribute to reduce the risk of misdiagnosis of MCS patients and consequently establish better therapeutic strategies.

Study 2. Resting functional connectivity in minimally conscious state *minus* versus *plus*

Minimally conscious state (MCS) patients have been sub-categorized in MCS+ and MCS-, respectively based on absence or presence of command-following, intelligible verbalization or intentional communication. We here aim to better characterize the functional neuroanatomy of MCS based on this clinical sub-categorization by means of resting state fMRI. Data were acquired in 292 MCS patients and a seed-based analysis was conducted on a convenience sample of 10 MCS+ patients, 9 MCS- patients and 35 HCS. We investigated the left and right frontoparietal networks, auditory network, default-mode network (DMN), thalamocortical connectivity and DMN between-network anticorrelations. We also employed an analysis based on regions of interest to examine interhemispheric connectivity and investigated inter-group differences in grey/white matter volume by means of voxel-based morphometry. We found a higher connectivity in MCS+ as compared to MCS- in the left frontoparietal network, specifically between the left dorso-lateral prefrontal cortex and left temporo-occipital fusiform cortex. No differences between patient groups were observed in the auditory network, right frontoparietal network, DMN, thalamocortical and interhemispheric connectivity, between-network anticorrelations and grey/white matter volume. These preliminary group-level results suggest that the clinical sub-categorization of MCS may involve functional connectivity differences in a language-related executive control network. MCS+ and MCS- patients are seemingly not differentiated by networks associated to auditory processing, perception of surroundings and internal awareness/self-mentation, nor by inter-hemispheric integration and structural brain damage.

1. Aim and hypotheses

The importance of brain metabolic function in the clinical sub-categorization of the minimally conscious state (MCS) was demonstrated in the previous study. In this second study, we aimed to better characterize the functional neuroanatomy of minimally conscious state (MCS) based on this sub-categorization into MCS+ and MCS- by means of resting state functional magnetic resonance imaging (fMRI). Apart from its non-invasive aspect, this technique is also more suitable than positron emission tomography to detect rapid changes in brain activation. Several studies further showed that resting state fMRI networks may contribute to the distinction of disorders of consciousness (DoC) (e.g., Demertzi et al., 2015).

According to Bruno et al. (2012) and results of our Study 1, the MCS+ sub-category presents higher glucose metabolism in a left fronto-temporo-parietal network. Moreover, previous studies in aphasic conscious patients showed an impairment of connectivity between structures in the left frontoparietal (FPN) (Kümmerer et al., 2013; Zhu et al., 2014). We consequently hypothesized a higher connectivity in MCS+ patients (i.e., who as compared to MCS- in this language-related executive control network (Smith et al., 2009).

We also investigated the default mode network (DMN), the auditory network and right FPN – which are known to differ between various altered states of consciousness (Crone et al., 2014; Demertzi et al., 2015; Di Perri et al., 2016; Estraneo et al., 2016; Laureys et al., 2000; Vanhaudenhuyse et al., 2011; Zheng et al., 2017) – to test whether the clinical sub-categorization of MCS might reflect differences in networks involved in internal awareness or self-related mentation, auditory processing and perception of surroundings respectively (Laird et al., 2011).

We further aimed at investigating whether the subcategories of MCS- and MCS+ are sustained by differences in interhemispheric connectivity in the networks of interest (Teki et al., 2013). Indeed, whether the reestablishment of left-right

hemisphere connectivity plays a role in residual language abilities in MCS+ patients is still unclear. Given that language is left hemisphere dominant (Broca, 1861; Klingbeil et al., 2017; McAvoy et al., 2016) and that recovery of language in aphasic conscious patients can involve compensatory mechanisms in the contralateral right hemisphere (Artzi et al., 2016; Heiss et al., 1999; Teki et al., 2013), the restoration of left-right hemisphere connections might play a particular role in the transition from MCS- to MCS+.

In addition, to control for the influence of anatomical deformations on functional connectivity changes (Demertzi et al., 2015; Di Perri et al., 2016), we investigated group differences in grey and white matter volume by means of voxel-based morphometry (VBM). In light of previous studies showing no unequivocal relationship between morphology and DoC (Di Perri et al., 2016; Tshibanda et al., 2009, Demertzi et al., 2015), we did not expect brain morphology to be significantly different between MCS subgroups.

Finally, we investigated DMN anticorrelations and thalamocortical functional connectivity, known to be different in patients with impaired consciousness as compared to healthy subjects (Di Perri et al., 2016; Estraneo et al., 2016; Kim et al., 2012; Zheng et al., 2017). In line with previous resting-state fMRI studies which did not show differences in anticorrelations between patients with various DoC (Di Perri et al., 2016; Zhou et al., 2011), we did not expect these markers to be significantly different between the MCS subgroups.

2. Methods

a. Participants

As in Study 1, patients were retrospectively included in this study after being behaviorally assessed with repeated Coma Recovery Scale-Revised (CRS-R)

(Giacino et al., 2004; Schnakers et al., 2008; Seel et al., 2010; Wannez, Heine, et al., 2017), which allowed us to categorize the patients as being MCS+ or MCS-. Exclusion criteria were: a) time post-injury less than 28 days, b) motion artifacts requiring sedation or anesthesia during scanning, c) motion parameters greater than 3 mm in translation and/or 3 degrees in rotation (leading to exclusion of subjects), d) large focal brain damage (i.e., more than 2/3 of one hemisphere) as stated by a certified neuroradiologist who was blind to patients' diagnosis (i.e., behavioral profile and research imaging findings), e) suboptimal segmentation and normalization as stated by a certified neuroradiologist, f) left-handedness. Moreover, HCS free of psychiatric or neurological history were included in the present research.

The study was approved by the Ethics Committee of the Faculty of Medicine in the University of Liège. Written informed consent to participate in the study was obtained from the HCS and from the legal surrogates of the patients.

b. Data acquisition

Resting-state fMRI: 300 T2*-weighted resting state fMRI volumes (Echo Planar Imaging sequence: 32 slices, repetition time = 2000 ms, echo time = 30 ms, field of view = 192×192 mm^2, flip angle = 78 degrees, voxel size = 3×3×3 mm^3) were acquired on a 3T scanner (Siemens Trio Tim, Munich, Germany), in one run of 10 minutes and 6 seconds.

Structural Imaging: For anatomical reference and further volumetric anatomical analysis, a high-resolution T1-weighted image was acquired per subject (see Study 1 for more details).

c. Data preprocessing

Resting-state fMRI: Data preprocessing was performed using Statistical Parametric Mapping 8 (SPM 8; www.fil.ion.ucl.ac.uk/spm). Preprocessing steps consisted of: slice-time correction, realignment, co-registration of functional on structural data, spatial normalization with the diffeomorphic anatomical registration through an exponentiated lie algebra (DARTEL) (Ashburner, 2007; Takahashi et al., 2010) and smoothing with Gaussian isotropic kernel (8 mm of full-width at half-maximum; FWHM). For the normalization procedure we used a study-template created with DARTEL obtained from patients and healthy subjects (Ashburner, 2007; Di Perri et al., 2013; Peelle, Cusack, & Henson, 2012). This template was used to minimize normalization difficulty as it decreases the degree of warping necessary for patient brains in the normalization step and reduces the likelihood of misclassification and normalization errors that can occur during the VBM process. For blood-oxygen-level-dependent (BOLD) noise reduction, we used the anatomical component-based noise correction method (Behzadi et al., 2007) as implemented in the *CONN* functional connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The anatomical component-based noise correction process derives principal components from noise regions of interest and includes them as nuisance parameters within the general linear models. The influence of noise was modeled as a voxel-specific linear combination of multiple empirically estimated noise sources. Precisely, the anatomical image for each subject was segmented into white matter, grey matter, and cerebrospinal fluid. White and cerebrospinal segments were eroded by one voxel to reduce partial voluming with grey matter (Chai et al., 2012). The eroded white matter and cerebrospinal fluid masks were used as noise regions of interest and their signals were deleted from the unsmoothed functional volumes to avoid additional risk of contaminating white matter and cerebrospinal fluid signals with grey matter signals. A temporal band-pass filter of 0,008-0,09 Hz was applied on the time series, to restrict the analysis to low frequency fluctuations which characterize functional MRI BOLD resting state activity as classically performed in seed-correlation analysis (Fox et al., 2005; Greicius et al., 2003). Remaining head

motion parameters (3 rotation and 3 translation parameters, plus another six parameters representing their first-order temporal derivatives) were regressed out. Regarding motion correction we used the artifact detection toolbox (ART; http://nitrc.org/projects/artifact_detect) for artifact detection and rejection, using a composite motion measure (largest voxel movement) with a "liberal" threshold (global threshold 9.0, motion threshold 2.0, use scan-to-scan motion and global signal). With this approach, a volume was defined as an outlier (artifact) if the largest voxel movement detected was above the specified thresholds. Specifically, an image was defined as an outlier (artifact) image if the head displacement in *x*, *y* or *z* direction was greater than 0.5 mm from the previous frame, or if the rotational displacement was greater than 0.02 radians from the previous frame, or if the global mean intensity in the image was greater than 3 standard deviations from the mean image intensity for the entire resting scan. Outliers in the global mean signal intensity and motion were subsequently included as nuisance regressors (i.e., one regressor per outlier within the first-level general linear model). In doing so, the temporal structure of the data was not disrupted.

Structural imaging: A T1 VBM analysis of brain structure for SPM8 (VBM8) was carried out using DARTEL as described in Study 1. The normalized images were visually controlled one by one in order to ensure that relative grey and white matter volumes were well preserved following spatial normalization. They were further overlaid on an MRI structural image to ensure that segmented tissue would be overlapping.

d. Statistical analysis

Resting-state fMRI: For measurement of fMRI resting state functional connectivity, a seed-based approach was performed using the *CONN* connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The seed-correlation analysis extracts fMRI BOLD time series from a region of interest (ROI; the seed) and determines the temporal correlation between this signal and the time series from all

other brain voxels. We investigated the left FPN, the right FPN, the auditory network, and the DMN correlations, known to be involved in language-related executive control, perception of surroundings, audition and internal awareness, respectively (Demertzi, Soddu, & Laureys, 2013; Laird et al., 2011; Smith et al., 2009; Stawarczyk et al., 2011). We further investigated DMN anticorrelations and functional thalamocortical connectivity, known to be related to consciousness and inter-network information integration (Di Perri et al., 2016; Estraneo et al., 2016; Kim et al., 2012; Zheng et al., 2017).

For each of them we defined two seeds as 5mm-radius spheres around peak coordinates of the two main nodes taken from the literature: left dorsolateral prefrontal cortex (DLPFC) and left inferior parietal lobule (IPL) were seeds for the left FPN; right DLPFC and right IPL were considered for the right FPN; auditory network seeds were left and right superior temporal gyrus (STG); medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) were seeds for the DMN. In order to avoid circularity (Kriegeskorte et al., 2009) and as previously described (Demertzi et al., 2015; Di Perri et al., 2016; Whitfield-Gabrieli & Nieto-Castanon, 2012), the seed coordinates were taken from the literature (table 5). Both seeds of each network were analyzed separately.

Table 5. Seed coordinates and references.

Networks	Seeds	Coordinates	References
Left FPN	Left DLPFC	*x*=-43 *y*=22 *z*=34	(Fair et al., 2009) for DLPFC (Rolls, Joliot, & Tzourio-Mazoyer, 2015) for IPL
	Left IPL	*x*=-43.1 *y*=-47 *z*=45.4	
Right FPN	Right DLPFC	*x*=43 *y*=22 *z*=34	
	Right IPL	*x*=46.3 *y*=-47.6 *z*=48.2	
Auditory network	Left STG	*x*=-44 *y*=-6 *z*=11	(Maudoux et al., 2012)
	Right STG	*x*=44 *y*=-6 *z*=11	
DMN	MPFC	*x*=-1 *y*=54 *z*=27	(Raichle et al., 2001)
	PCC	*x*=0 *y*=-52 *z*=27	
Thalamocortical	Left thalamus	*x*=-8 *y*=-20 *z*=6	(Kinomura et al., 1996; Laureys et al., 2000)
	Right thalamus	*x*=8 *y*=-20 *z*=6	

FPN: fronto-parietal network; DMN: default mode network; DLPFC: dorso-lateral prefrontal cortex; IPL: inferior parietal lobule; STG: superior temporal gyrus; MPFC: medial prefrontal cortex; PCC: posterior cingulate cortex.

The time series of each seed were used to estimate whole-brain correlation *r* maps which were then converted to normally distributed Fisher's *z* transformed

correlation maps to allow for group-level comparisons. In the matrix we identified the positive correlations for each group (MCS+, MCS- and healthy control subjects; HCS) and the differences between MCS+ and MCS-, MCS+ and HCS, MCS- and HCS. Anticorrelations were generated by computing the averaged time series in both DMN seeds (MPFC and PCC). The time series were then compared at the whole brain level using Pearson correlation, generating a statistical map of the average correlation coefficient for each voxel and the average signal of the seeded regions (Di Perri et al., 2016).

We further employed a ROI to ROI analysis using the same seeds as for the seed-voxel analysis, in order to investigate functional connections for each network between the right and left hemispheres in subject groups, as previously done (McKenna et al. , 2015). Each ROI from one side was correlated with all ROIs from the other side. Results were considered statistically significant at $p < 0.05$ family wise error (FWE) corrected at cluster level, with clusters made of voxels surviving a $p < 0.001$ (whole brain level) (Woo, Krishnan, & Wager, 2014).

Structural-MRI: We investigated patient group differences in grey and white matter volume by means of VBM using the grey matter and white matter segments previously obtained by the DARTEL segmentation, as previously described (Demertzi et al., 2015; Di Perri et al., 2016). In the matrix we identified the differences between MCS+ and MCS-, MCS+ and HCS, MCS- and HCS. Results were considered significant at $p < 0.05$ false discovery rate (FDR) corrected at voxel-level.

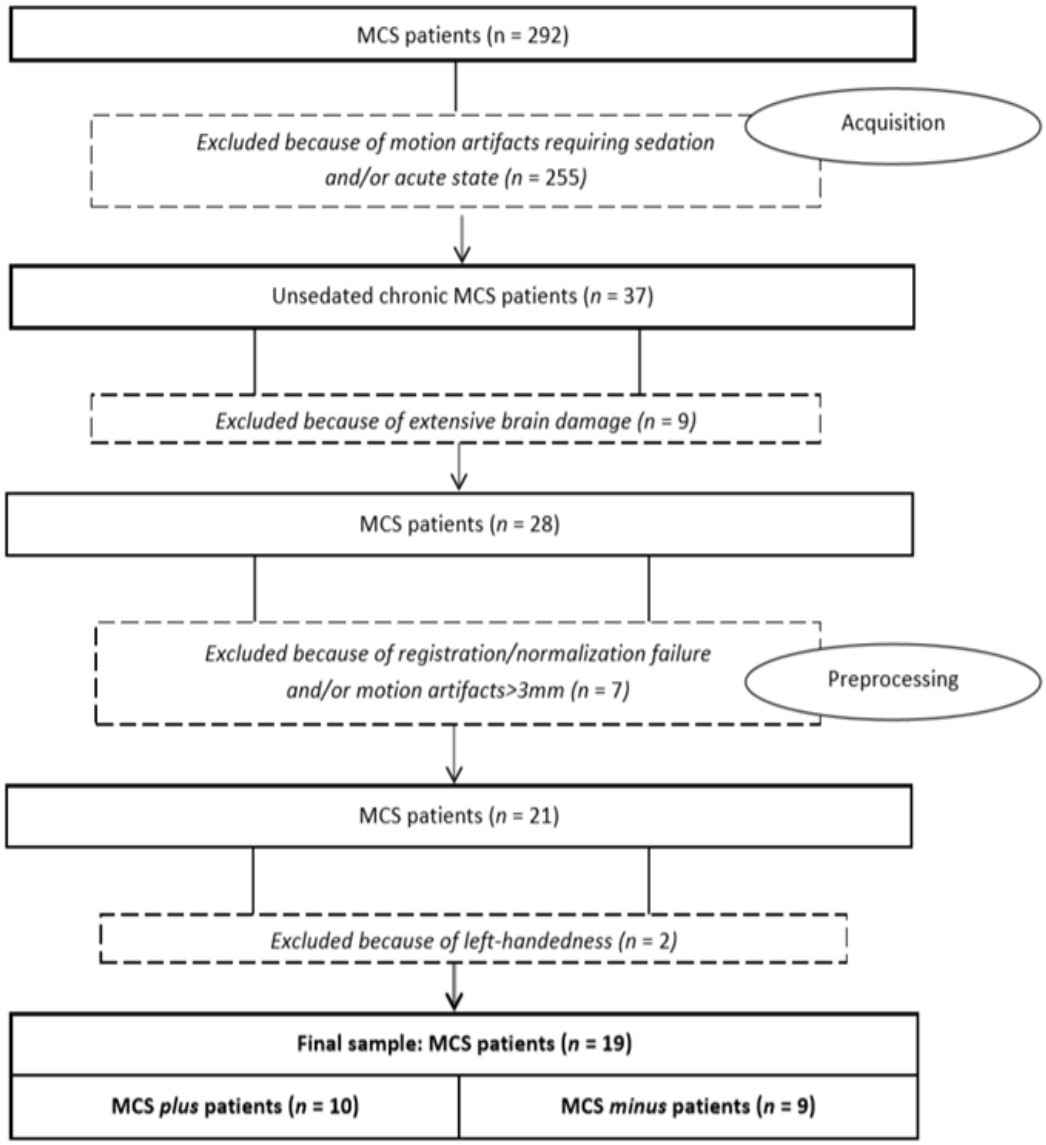

Figure 6. *Flowchart: patient selection based on exclusion criteria.MCS: minimally conscious state.*

3. Results

a. Patients

Between October 2009 and June 2016, 292 brain-damaged patients subsequently diagnosed as MCS were admitted into the University Hospital of Liège. Following the exclusion criteria (figure 6), the analysis focused on a convenience sample of 19 right-handed MCS patients: 9 MCS- (2 women; aged 37 ± 14 years) and 10 MCS+ (2 women; aged 39 ± 12 years) patients (table 6). Age and time post-injury did not differ between groups (Mann-Whitney U test: $p = 0.66$ and $p = 0.97$ respectively), neither did gender and etiology (binomial test: respectively $p = 0.91$ and $p = 0.25$ for traumatic versus non-traumatic brain injury, i.e. cerebrovascular accident, anoxia and epilepsy). Thirty-five HCS were also recruited; again age and gender did not differ between groups (respectively Mann-Whitney U test: $p = 0.21$ and binomial test: $p = 0.36$ – 24 women, aged 41 ± 15 years).

b. Resting-state fMRI

Table 7 describes the cerebral areas that are functionally connected to the investigated seeds, respectively in HCS, MCS+ patients and MCS- patients. Table 8 describes the cerebral areas showing significant between-group differences for each seed. More details are reported in appendix III (table S1 and table S2).

Left frontoparietal network (FPN)

In HCS, the left DLPFC and left IPL were functionally connected to the lateral frontal cortex (superior, middle and inferior frontal gyrus – more on the left side), bilateral lateral inferior temporal cortex, precuneus, supramarginal and angular gyrus (mainly on the left side), insulae, supplementary and presupplementary motor area [figure 7A, bottom row]. In MCS+ the left DLPFC and IPL were functionally

connected to the left lateral frontal cortex, left inferior temporal cortex, left superior temporal gyrus and angular/supramarginal gyrus, the precuneus, the mesial frontal cortex and the supplementary motor area mainly on the left side [figure 7A, middle row]. In MCS- the left DLPFC and IPL appeared functionally connected to the lateral frontal cortex bilaterally, to the left supramarginal/angular gyrus and to some extent to the precuneus and presupplementary motor area [figure 7A, upper row].

MCS+ (compared to MCS-) showed higher connectivity between the left DLPFC and left temporo-occipital fusiform cortex [figure 7B and 7C for single subject data].

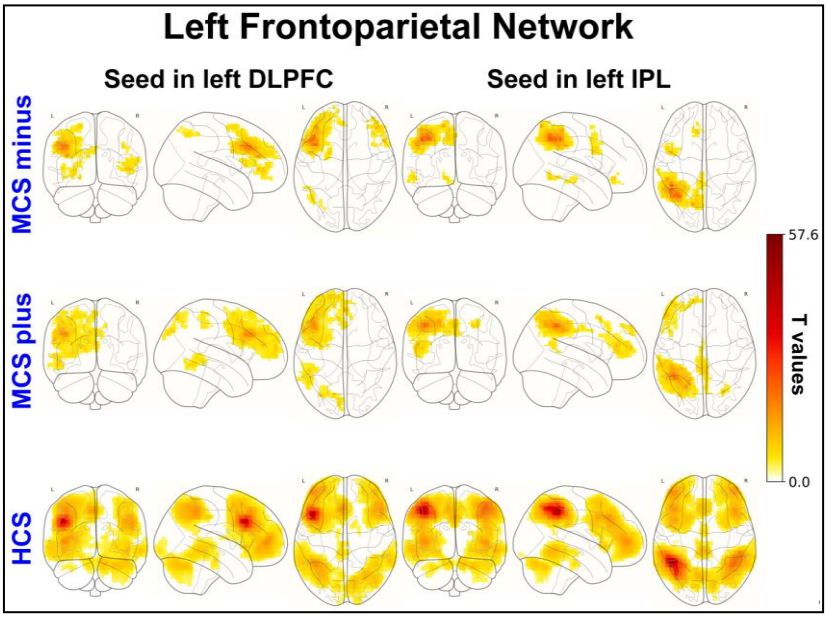

Figure 7A. *Correlation between the left DLPFC (left column), left IPL (right column) and the time series from all other brain voxels in MCS- (upper row), MCS+ (middle row) and HCS (bottom row). Statistical maps are thresholded at p < 0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p < 0.001(whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The color bar indicates T values. This figure was displayed in neurological convention. DLPFC: dorsolateral prefrontal cortex, IPL: inferior parietal lobule, MCS: minimally conscious state, HCS: healthy control subjects.*

HCS showed increased connectivity compared to MCS+ between the left DLPFC and right middle frontal gyrus and between left IPL, right angular gyrus and lateral middle/inferior frontal gyri [appendix III – figure S1, bottom row]. HCS showed increased connectivity than MCS- between left DLPFC and left inferior

temporal gyrus and the inferior parietal cortex, as well as between left IPL and right superior temporal gyrus, right angular gyrus and right middle/inferior frontal gyrus [appendix III – figure S1, upper row].

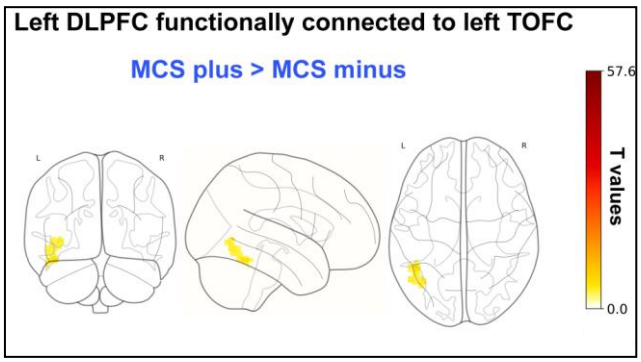

Figure 7B. *Difference between MCS- and MCS+ according to the correlation between the left DLPFC and the time series from all other brain voxels. Statistical maps are thresholded at p < 0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p < 0.001(whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The color bar indicates T values. This figure was displayed in neurological convention. DLPFC: dorsolateral prefrontal cortex, TOFC: temporo-occipital fusiform cortex, MCS: minimally conscious state.*

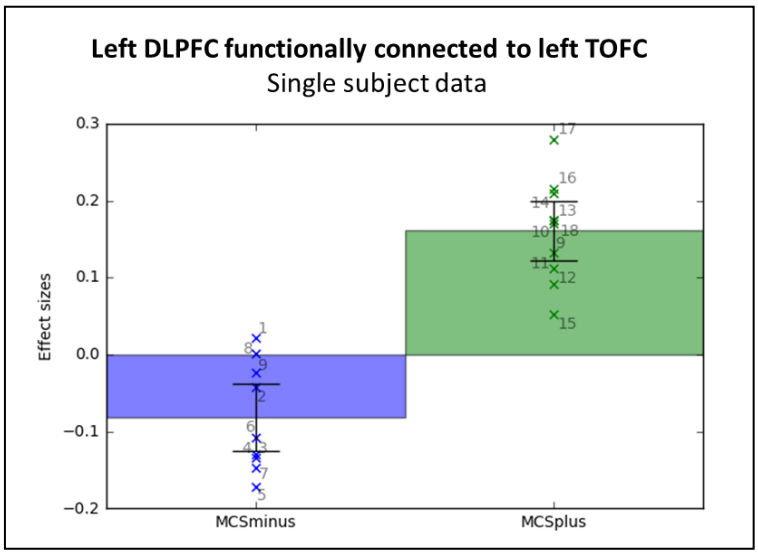

Figure 7C. *Comparison of the correlation of the voxel timeseries between the left dorsolateral prefrontal cortex (DLPFC) and the left temporo-occipital fusiform cortex (TOFC) between MCS- and MCS+, averaged over all significant clusters. The first bar represents mean contrast estimates with 90% confidence interval in patients in MCS (minimally conscious state) minus (blue); the second bar represents mean contrast estimates with 90% confidence interval in MCS+ patients (green). Crosses represent single subject average correlation values, with the number referring to specific subjects as shown in table 5. Statistical maps are thresholded at p < 0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p < 0.001(whole-brain level). MCS: minimally conscious state.*

Table 6. Demographic and clinical data of MCS patients.

Patient	Age	Sex	Etiology	Months since onset	CRS-R best total score	Auditory functions	Visual functions	Motor functions	Oro-motor functions	Commu-nication	Arousal	Final diagnosis
1	66	M	CVA	1,5	12	2	3	5	2	0	2	MCS-
2	27	M	TBI	12	9	1	3	2	2	0	2	MCS-
3	19	F	TBI	26	10	1	3	2	2	0	2	MCS-
4	37	M	CVA	60	10	1	3	3	2	0	2	MCS-
5	30	M	TBI – Anoxia	14	9	0	1	5	2	0	1	MCS-
6	28	M	TBI – Anoxia	3	7	1	3	2	1	0	2	MCS-
7	43	M	Anoxia	21	8	2	3	1	2	0	2	MCS-
8	45	F	TBI	8	8	2	3	2	1	0	2	MCS-
9	38	M	Anoxia	9	9	1	4	1	1	0	2	MCS-
10	34	F	TBI	96	12	3	3	2	2	0	2	MCS+
11	29	M	TBI	8	11	3	3	3	2	1	2	MCS+
12	50	M	TBI	8	13	3	4	2	2	0	2	MCS+
13	51	M	Epilepsy	2	14	3	5	2	3	1	2	MCS+
14	54	M	TBI	1,5	12	3	3	4	3	0	2	MCS+
15	29	M	TBI	1,5	9	3	4	5	2	1	2	MCS+
16	57	M	Anoxia	15	7	3	0	2	2	0	2	MCS+
17	30	F	TBI	90	8	3	0	2	2	0	2	MCS+
18	34	M	TBI	44	8	3	0	2	2	0	2	MCS+
19	23	M	TBI	22	10	3	3	3	3	0	2	MCS+

Multiple Coma Recovery Scale-Revised (CRS-R) assessments were performed. The best total score and best subscale scores among all assessments were retained.
M: male; F: female; CVA: cerebrovascular accident; TBI: traumatic brain injury; MCS: minimally conscious state.

Table 7. Network connectivity in MCS- patients, MCS+ patients and HCS.

	Left FPN	Right FPN	AN	DMN
MCS-	(Figure 7A upper row) Bilateral lateral frontal cortex Precuneus Left supramarginal gyrus Left angular gyrus Presupplementary motor area	(Figure 8 upper row) Right lateral frontal cortex Precuneus Right supramarginal gyrus Right angular gyrus Supplementary motor area	(Figure 9 upper row) Insulae Sensorimotor cortex	(Figure 10 upper row) Anterior cingulate/mesio-prefrontal cortex Posterior cingulate cortex/precuneus Temporo-parietal junctions Superior frontal gyrus Angular gyrus
MCS+	(Figure 7A middle row) Left lateral frontal cortex Left inferior temporal cortex Left superior temporal gyrus Supramarginal gyrus Angular gyrus Precuneus Mesial frontal cortex Supplementary motor area	(Figure 8 middle row) Right lateral frontal cortex Precuneus Right supramarginal gyrus Right angular gyrus Supplementary motor area	(Figure 9 middle row) Insulae Sensorimotor cortex	(Figure 10 middle row) Anterior cingulate/mesio-prefrontal cortex Posterior cingulate cortex/precuneus Temporo-parietal junctions Superior frontal gyrus Angular gyrus
HCS	(Figure 7A bottom row) Lateral frontal cortex Bilateral lateral inferior temporal cortex Precuneus Supramarginal gyrus Angular gyrus Insula Supplementary motor area	(Figure 8 bottom row) Lateral frontal cortex Lateral temporal cortex Mesial frontal cortex Precuneus Supramarginal gyrus Angular gyrus	(Figure 9 bottom row) Insulae Superior temporal gyri Sensorimotor cortex Supplementary motor cortex Supramarginal gyri	(Figure 10 bottom row) Anterior cingulate/mesio-prefrontal cortex Posterior cingulate cortex/precuneus Temporo-parietal junctions Angular gyri Mesial temporal cortex Superior lateral temporal cortex

FPN: fronto-parietal network ; AN: auditory network; DMN: default mode network; MCS: minimally conscious state; HCS: healthy control subjects.

Table 8. Cerebral areas showing significant between-group differences in functional connectivity.

	Left FPN	Right FPN	AN	DMN
MCS+ > MCS-	Left temporo-occipital fusiform cortex (figure 7B)	/	/	/
HCS > MCS+	Right middle frontal gyrus Right temporal pole Right angular gyrus Lateral middle/inferior frontal gyri	Left middle frontal gyrus Inferior parietal cortex Left angular gyrus Mesio-frontal cortex	Insula Sensorimotor cortex Mesio-frontal cortex	Mesial prefrontal cortex Precuneus Temporal poles
HCS > MCS-	Left inferior temporal gyrus Inferior parietal cortex Right superior temporal gyrus Right angular gyrus Right middle/inferior frontal gyri	Left angular gyrus Mesio-frontal cortex	Insula Sensorimotor cortex Mesio-frontal cortex	Mesial prefrontal cortex Precuneus Temporal poles Left angular gyrus

FPN: frontoparietal network ; AN: auditory network; DMN: default mode network; MCS: minimally conscious state; HCS: healthy control subjects.

Right frontoparietal network (FPN)

In HCS, the right DLPFC and IPL were functionally connected to the lateral frontal cortex (more extensively on the right side), to the lateral temporal cortex, the precuneus, mesial frontal cortex and supramarginal/angular gyrus (more extensively on the right side) [figure 8, bottom row]. In MCS+ and MCS-, the right DLPFC and IPL were functionally connected to the right supramarginal/angular gyrus, right lateral frontal cortex, and supplementary motor area [figure 8, upper and middle row]. MCS+ showed to some extent connectivity also in the mesial right frontal cortex and precuneus [figure 8, middle row]. No differences were detected between MCS+ and MCS-.

HCS showed higher connectivity than MCS+ in left middle frontal gyrus, inferior parietal cortex, left angular gyrus [appendix III – figure S2, bottom row]. HCS showed higher connectivity than MCS- in the left angular gyrus and mesial frontal cortex [appendix III – figure S2, upper row].

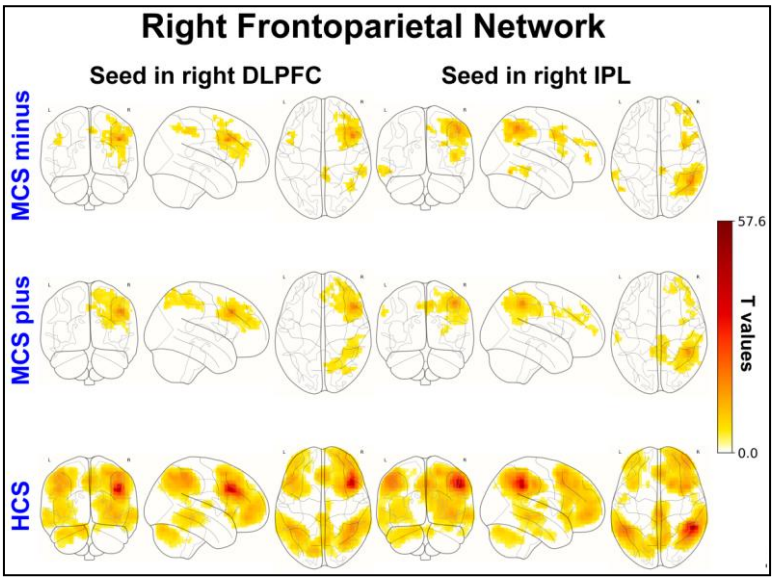

Figure 8. *Correlation between the right DLPFC (left column), right IPL (right column) and the time series from all other brain voxels in MCS- (upper row), MCS+ (middle row) and HCS (bottom row). Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The color bar indicates T values. This figure was displayed in neurological convention. DLPFC: dorsolateral prefrontal cortex, IPL: inferior parietal lobule, MCS: minimally conscious state, HCS: healthy control subjects.*

Auditory network

In HCS, the right and left superior temporal gyri (STG) were functionally connected to the insulae, superior temporal gyri, sensorimotor cortex, supplementary motor cortex, supramarginal gyri [figure 9, bottom row]. In MCS+ and MCS-, right and left STG were functionally connected to the insulae, and to a certain extent sensorimotor cortex [figure 9, upper and middle row]. No significant differences were observed between MCS+ and MCS-.

HCS showed higher connectivity than MCS+ and MCS- in the insulae, sensorimotor cortex and mesial frontal cortex [appendix III – figure S3].

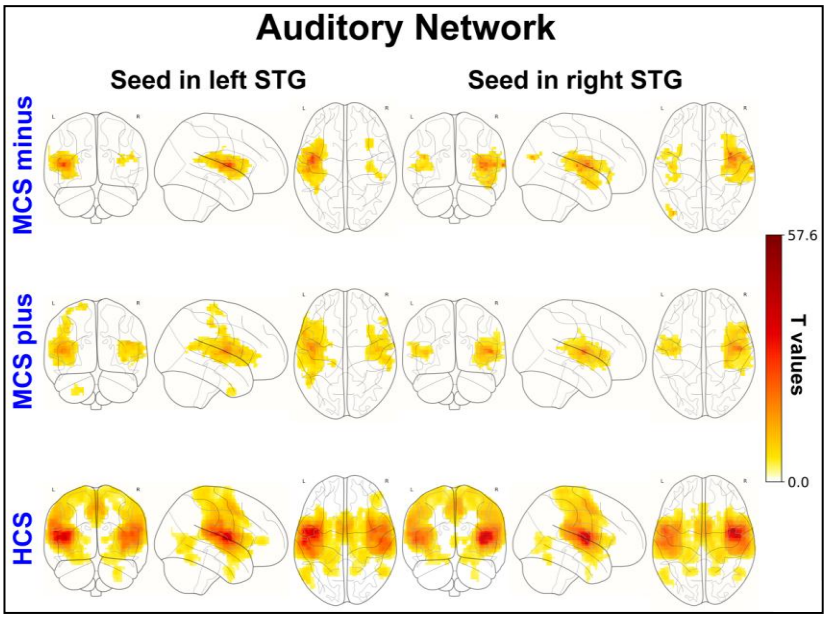

Figure 9. *Correlation between the left STG (left column), right STG (right column) and the time series from all other brain voxels in MCS- (upper row), MCS+ (middle row) and HCS (bottom row). Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The color bar indicates T values. This figure was displayed in neurological convention. STG: superior temporal gyrus, MCS: minimally conscious state, HCS: healthy control subjects.*

Default mode network (DMN)

In HCS, the MPFC and the PCC seeds showed connectivity with the precuneus, temporo-parietal junctions, angular gyri, mesial temporal cortex and superior lateral temporal cortex [figure 10, bottom row]. In MCS+ and MCS-, the MPFC appeared functionally connected to the superior frontal gyrus and the PCC with the precuneus, temporo-parietal junctions and angular gyrus (in MCS+) [figure 10, upper and middle row]. No differences between MCS+ and MCS- were observed.

HCS showed higher connectivity than MCS+ in MPFC/mesial prefrontal cortex, PCC/precuneus and temporal poles [appendix III – figure S4, bottom row]. HCS showed higher connectivity than MCS- more extensively in MPFC/mesial prefrontal cortex, PCC/precuneus and temporal poles and also in the left angular gyrus [appendix III – figure S4, upper row].

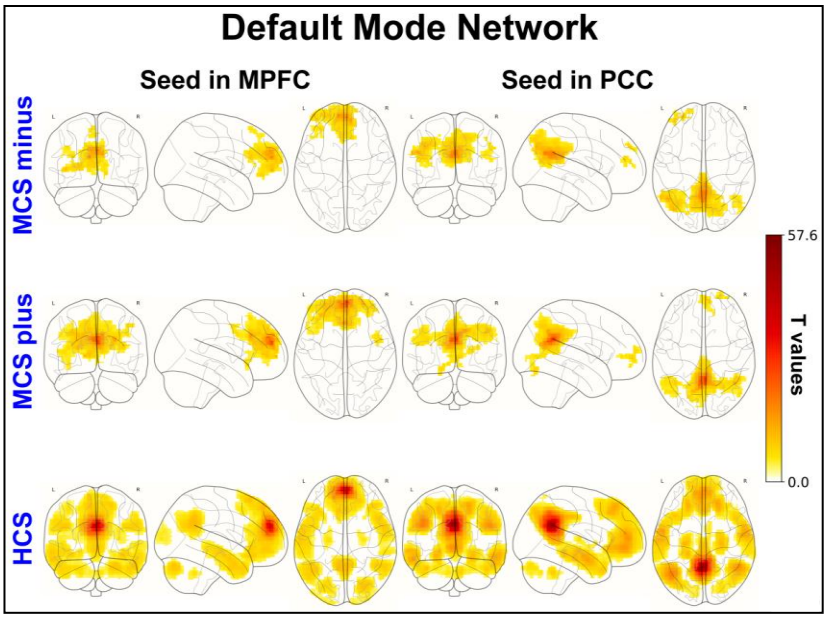

Figure 10. *Correlation between the MPFC (left column), PCC (right column) and the time series from all other brain voxels in MCS- (upper row), MCS+ (middle row) and HCS (bottom row). Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The color bar indicates T values. This figure was displayed in neurological convention. MPFC: medial prefrontal cortex, PCC: posterior cingulate cortex, MCS: minimally conscious state, HCS: healthy control subjects.*

Thalamocortical connectivity

In the HCS the left and right thalamus were functionally connected to the MPFC, PCC/precuneus, insulae, orbitofrontal cortices and left angular gyrus (appendix III – figure S8, upper row). HCS compared to MCS- patients showed increased connectivity between the thalamus and the superior frontal gyrus, the cingulate cortex, precuneus and MPFC (appendix III – figure S8, middle row). HCS compared to MCS+ patients showed higher functional connectivity between the thalamus and MPFC, angular/supramarginal gyrus (appendix III – figure S8, bottom row). No differences were observed between MCS+ and MCS-.

Interhemispheric connectivity

In the ROI to ROI connectivity analysis HCS showed higher connectivity as compared to MCS- patients between right and left STG, right and left IPL and between MPFC and PCC. HCS showed higher connectivity as compared to MCS+ patients between right and left STG, right and left DLPFC, right and left IPL and between MPFC and PCC (appendix III – table S3). No differences were observed between MCS+ and MCS-.

DMN anticorrelations

In HCS compared to MCS- and MCS+ groups anticorrelations have been observed in the lateral frontal and parietal hemispheres, insulae, supplementary/presupplementary motor regions and cuneus (appendix III – figure S9). A similar pattern of anticorrelations was observed for the MCS- and MCS+ groups.

c. Structural MRI

MCS- and MCS+ patients showed reduced grey matter volume as compared to HCS broadly involving the fronto-temporo-parietal regions and the cerebellum (appendix III – figure S6). Patients also showed widespread white matter decrease as compared to HCS, involving the corpus callosum, mesencephalon, occipital

regions and lateral fronto-parieto-temporal regions mainly on the left hemisphere (appendix III – figure S7). No differences in grey and white matter were detected between MCS+ and MCS-.

4. Discussion

In this study, we aimed to better characterize the functional neuroanatomy of MCS subcategories (Bruno et al., 2011) by means of resting-state fMRI. As expected, for all four networks, as well as for thalamocortical connectivity and between-network anticorrelations, the HCS showed significantly higher functional connectivity than MCS- and MCS+ patients. This is in line with a large amount of literature showing impaired connectivity in patients compared to HCS in the left and right FPN, the auditory network, and the DMN (Demertzi et al., 2015; Di Perri et al., 2016; Kirsch et al., 2017), thalamocortical connectivity (Estraneo et al., 2016; Zheng et al., 2017) and between-network anticorrelations (Di Perri et al, 2016). In addition we found differences between patient groups only in the left FPN, a language-related executive control network (Smith et al., 2009). Specifically, we found higher connectivity between the left DLPFC and the left temporo-occipital fusiform cortex in MCS+ as compared to MCS- patients.

Such a difference in functional connectivity detected between patient groups corroborates previous literature associating the left FPN with language-related control (Laird et al., 2011; Smith et al., 2009) such as semantic control (Xu et al., 2016). For example, Zhu et al. (2014) showed impairment of this network in patients presenting language alterations. The authors investigated resting state fMRI and clinical evaluation of language function in AC post-stroke patients and found reduced functional connectivity between the left FPN and the right middle frontal cortex, medial frontal cortex, and right inferior frontal cortex in their patients. They

also found a significant association between the degree of connectivity breakdown of the left FPN and the patients' comprehension abilities, suggesting that stroke lesions might have influenced language comprehension by altering within-network intrinsic connectivity (Zhu et al., 2014). Furthermore, reorganization of this functional network was associated to the recovery of language function, as shown through greater improvement in language function after stroke recovery (Sharp et al., 2010; Van Hees et al., 2014).

Furthermore, these main findings are consistent with a previous FDG-PET study (Bruno et al., 2012) showing metabolic impairment in MCS- as compared to MCS+ patients in a fronto-temporo-parietal network involving Broca's and Wernicke's regions, left premotor, left caudate, and post-/pre-central cortices. We therefore suggest that the proposed sub-categorization of MCS based on command-following, intelligible verbalization and intentional communication (Bruno et al., 2011) is supported by differences in resting state functional connectivity in the left FPN. In particular, the alteration between the left DLPFC and the left temporo-occipital fusiform cortex (Brodmann Area 37) in MCS- involves regions that have been associated with language processing and control of verbal information. The left temporo-occipital fusiform cortex has been identified as an "extended Wernicke's area" (Ardila, Bernal, & Rosselli, 2016), which is mainly dedicated to receptive language abilities. This region is also considered to link visual and semantic information (Ardila, Bernal, & Rosselli, 2015; Vigneau et al., 2006). The left temporo-occipital fusiform cortex has furthermore been shown to be involved in semantic categorization and matching of visual material (Adams & Janata, 2002; Binder et al., 1997; Damasio et al., 2001), but also in word versus non-word reading (Cohen et al., 2002; Fiez et al., 1993). In sum, connectivity alterations in this area might signal language deficits in MCS- patients, which in turn might prevent them from following commands, verbalization and intentional communication.

In the present study, we did not find between-patient group differences in functional connectivity of the right FPN and the auditory network, suggesting that command-following, intelligible verbalization and intentional communication

capacities that distinguish the two subgroups cannot be explained by the functional status of these networks (Laird et al., 2011). Nor did we find any difference in DMN correlations, suggesting that the MCS sub-categorization might not be related to internal awareness/self-related mentation known to be supported by the DMN (Demertzi et al., 2015; Vanhaudenhuyse et al., 2011). Taken together, our preliminary findings show that the clinical MCS- and MCS+ sub-categorization involves differences in networks related to language processing, and that language residual abilities are an important characteristic of the MCS+ subcategory.

The DMN is linked to cognitive processes related to internal thoughts, mind wandering and autobiographical memory (Stawarczyk et al., 2011), as well as to conscious awareness more generally (Demertzi, Soddu, et al., 2013). Some resting state fMRI studies suggest that activity of the DMN is reduced as a function of the level of impairment of consciousness, with the strongest reductions of activity observed in coma and UWS (Di Perri et al., 2016; Heine et al., 2012). The above findings suggest that MCS+ and MCS- may differ in language processing, but not in their internal thoughts or mind-wandering, despite the fact that internal thoughts might be linked to inner-speech and therefore to language processing (Alderson-Day & Fernyhough, 2015; Corballis, 2013; Jones & Fernyhough, 2007). A study in HCS showed that only 17% of resting-state experiences were language-based (Delamillieure et al., 2010), whilst other dominant types of mental activities were visual mental imagery (35%), somato-sensory awareness (7%), inner musical experience (6%) and mental manipulation of numbers (1%). Our results may therefore imply that these latter mental activities would be similarly impaired in MCS- and MCS+ patients, and that the clinical sub-categorization of MCS patients could reflect a difference in language rather than in conscious awareness. We should also note that such a dissociation between connectivity of DMN and left FPN was found in different cases of language impaired conditions, such as logopenic primary progressive aphasia (Humphreys et al., 2015; Lehmann et al., 2016; Whitwell et al., 2015).

The fact that we did not find differences between patient groups in interhemispheric connectivity suggests that recovery of command-following, intelligible verbalization and/or intentional communication in severely brain injured patients is not related to differences in interhemispheric connectivity. These results are in line with a recent study showing that recovery of language function relies on intact left intrahemispheric functional connectivity (Siegel et al., 2016). Further studies are needed in order to specify the lateralization of command-following, intelligible verbalization and intentional communication in a healthy brain, but also to better investigate possible language mechanisms in severely brain injured patients.

Our findings regarding anticorrelation patterns in patients and HCS align with previous studies reporting a rich interplay between internal and external modes of functioning which has been linked to conscious behavior (Di Perri et al., 2016). It has also been shown that the degree to which DMN and FPN (internal and external awareness networks) are anticorrelated is linked to cognitive function (Leech et al., 2011). Stronger anticorrelations would therefore reflect a better capacity to switch between internal and external modes of attention, which sustains cognitive abilities necessary for conscious awareness (Di Perri et al., 2016; Leech et al., 2011). The lack of differences in anticorrelations between MCS subcategories is further consistent with a recent study showing no significant differences between various DoC (Di Perri et al., 2016).

With respect to structural damages, we did not observe differences in grey and white matter volume between MCS- and MCS+ patients using VBM. This is consistent with previous studies (Demertzi et al., 2015; Di Perri et al., 2016; Tshibanda et al., 2009) and suggests that the identified differences in functional connectivity are not related to morphological differences.

Our study design is not without limitations. Our sample size is limited to 19 patients. Due to this small sample and its heterogeneity, any generalizability of our results (including negative findings) should be done with extreme caution and our present study should be considered a preliminary study. Nevertheless, it should be

taken into account that valid resting state functional brain images in this patient population are difficult to obtain given the patients' tendency to move in the scanner, the high probability of severe brain lesions distorting brain morphometry, as well as metal and hemosiderine artifacts, which lead to a high number of patients being excluded from the study (see flowchart). Another point to keep in mind is that, whilst the most up-to-date clinical diagnostic criteria have been applied to avoid misdiagnosis (Wannez, Heine, et al., 2017), an isolated difference in language domain between the two patient groups cannot be drawn with certainty. Lack of command-following could for example be influenced by motor impairment or arousal fluctuations. Finally, our interpretations are based on the assumption of a close correspondence between resting state networks and the networks involved in active paradigms (Smith et al., 2009), and therefore should be cautiously interpreted (e.g., auditory networks observed during rest and during active listening tasks may not necessarily be exactly the same).

In conclusion, the proposed subcategories of MCS (Bruno et al., 2011), based on residual language-related behavioral abilities, showed a different functional neuroanatomy as detected by resting-state fMRI. Patients in MCS- compared to MCS+ showed impaired connectivity in the left FPN, a network involved in language-related executive control. Specifically, in MCS+ the left DLPFC was significantly more connected to the left temporo-occipital fusiform cortex, a region involved in visuo-semantic language integration. No functional connectivity differences between patient groups were observed in the auditory network, right FPN, DMN correlations and anticorrelations, nor in thalamocortical loop, inter-hemispheric connectivity and grey/white matter volume. These findings suggest that the proposed clinical sub-categorization of MCS patients (Bruno et al., 2011) reflects differences in residual language-related functional connectivity, and that it is seemingly not influenced by auditory processing, perception of surroundings, internal awareness/self mentation, nor by the level of integration between both hemispheres and brain structure. These preliminary results are of clinical relevance and might help to reduce the misdiagnosis of minimally conscious patients.

Study 3. The reappearance of command-following: A neuroimaging longitudinal multiple case series

The recovery of patients with disorders of consciousness is a real challenge, especially at the chronic stage. After a severe brain injury, patients can regain some slight signs of consciousness, while not being able to functionally communicate. This minimally conscious state (MCS) entity has been divided into MCS- and MCS+, respectively based on the absence or presence of language-related signs of consciousness. In this series of cases we aim to describe retrospectively the longitudinal recovery of specific language-related behaviors using neuroimaging measurement in severely brain-injured patients. Among 209 chronic MCS patients admitted to our center from 2008 to 2018, 19 were assessed at two time points by means of repeated Coma Recovery Scale-Revised, fluorodeoxyglucose-positron emission tomography and structural magnetic resonance imaging. Three of them were diagnosed as MCS- during their first stay and had recovered command-following when they were reassessed. As compared to their first assessments, when the three patients were in a MCS+, they showed less hypometabolism and/or higher grey matter volume in brain regions such as the precuneus and thalamus, as well as the left caudate and temporal/angular cortices known to be involved in various aspects of semantics. According to these preliminary results, the reappearance of language-related behaviors was concomitant with the recovery of metabolism and grey matter in neural regions that have been associated with self-consciousness and language processing. Prospective studies should be conducted to deepen our understanding of the neural correlates of the recovery of language-related behaviors in chronic MCS.

1. Aim and hypotheses

So far the neural correlates of the minimally conscious state (MCS) sub-categorization were reported through diverse cross-sectional studies. Given the clinical relevance of such patient sub-categorization, we aimed to retrospectively examine the trajectory of recovery of individual patients when followed longitudinally. We demonstrate in three MCS patients the transition from the MCS- to MCS+ using repeated neuroimaging and behavioral assessments. Fluorodeoxyglucose-positron emission tomography (FDG-PET) was particularly indicated due to its high sensitivity and non-frequent necessity of sedation, and voxel-based morphometry (VBM) was performed to further assess grey matter structure damages at the individual level. Based on the previously described studies, we hypothesize that these patients would show less impaired language-related areas following the recovery of language-related signs of consciousness (i.e., when in MCS+ compared to MCS-), at least using FDG-PET.

2. Methods

Between 2008 and 2018, 209 brain-damaged patients subsequently diagnosed as MCS were admitted into the University Hospital of Liège, including 19 patients who were assessed at two time points using neuroimaging techniques and repeated Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004; Wannez, Heine, et al., 2017). Among them, three chronic patients (age: 23-37 years-old, two traumatic brain injuries, time since onset: 10 months to 5 years) were diagnosed as MCS- during their first week of assessments. They later recovered command-following when reassessed during a second week of evaluations (26 to 31 months later). The

study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège and written informed consents for study participation and data publication have been obtained from the patients' legal representatives as well as from the healthy conscious subjects (HCS).

FDG-PET data were acquired and preprocessed as described in Study 1. The design matrices included the two repeated scans of each patient and the scans of HCS (n = 34, see Study 1). Sample t-tests were used to assess the fluoro-deoxyglucose metabolism differences between patients and HCS. Results were considered significant at $p < 0.05$ false discovery rate (FDR)-corrected.

Structural magnetic resonance imaging (MRI) data were also acquired and preprocessed as described in Study 1. Data were modeled using a factorial design with the total intracranial volume as covariate. An exclusive mask of the cerebrospinal fluid mask was used. A design matrix was constructed for each patient, including the two patient's scans (pre and post) and the scans of MRI-specific HCS (n = 36, see Study 1). Sample t-tests were conducted to assess the grey matter differences between patient and controls. Results were considered significant at FDR-corrected $p < 0.05$ voxel-wise over the whole brain.

Statistical analyses identified: a) brain areas showing hypometabolism (as compared with HCS) when the patient was in MCS-; b) brain areas showing hypometabolism when the patient was in MCS+; c) brain areas showing less hypometabolism or grey matter impairment when the patient was in MCS+ as compared to the scan when the patient was in MCS-.

3. Results

Demographical and neuroimaging results are presented in figure 11 and table 9. Behavioral (i.e., CRS-R sub-scores) and neuroimaging details are reported in appendix IV (supplementary material 1 and 2).

At time 1, the left-handed case 1 presented hypometabolism in the bilateral angular, fusiform and middle frontal gyri, left calcarine gyrus and right thalamus, cerebellum, inferior occipital and middle temporal gyri. When this patient was able to respond to simple commands 27 months later, we identified a significant recovery of metabolism in the bilateral angular and middle frontal gyri, left precuneus, middle occipital and calcarine gyri, right inferior occipital gyrus and cerebellum. Grey matter volume did not significantly increase or decrease between both examinations.

At time 1, case 2 presented hypometabolism mostly in the left superior medial gyrus and temporo-parieto-occipital cortex. Thirty-one months later, we observed command-following, along with a significant increase of metabolism in the left temporal lobule, cerebellum and superior medial gyrus, as well as the thalamus. Grey matter volume was shown to be significantly increased in MCS+ than in MCS- in the bilateral caudate and the left fusiform, angular and middle/inferior temporal gyri.

Finally, at time 1, case 3 presented hypometabolism in the left middle frontal and temporal gyri, left inferior parietal lobule, left rolandic operculum and right thalamus. When he had recovered command-following 26 months later, we identified a recovery of metabolism in the bilateral caudate and the left middle frontal gyrus. Grey matter volume was also significantly more important in bilateral parahippocampal gyri, in the left inferior and superior temporal cortex, caudate, inferior parietal lobule, precuneus and frontal cortex, as well as in the right thalamus, middle frontal and temporal cortex.

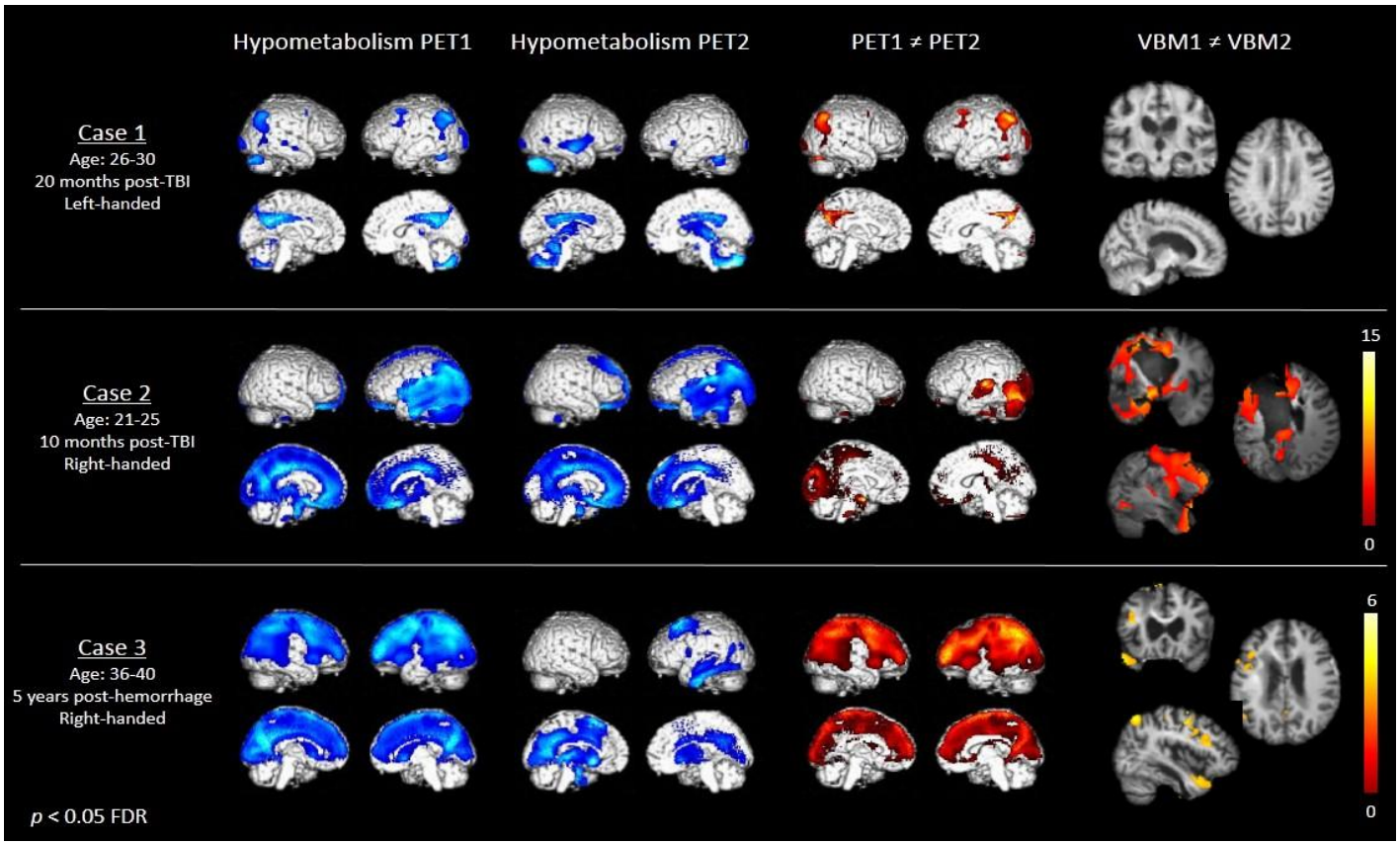

Figure 11. *Neuroimaging results in the three patients. Demographical data (1st column), cerebral hypometabolism at time 1 and time 2 (2nd and 3rd column in blue), recovery of metabolism (4th column in red) as assessed with glucose positron emission tomography (PET), as well as recovery of grey matter volume (fifth column) as assessed with MRI voxel-based morphometry (VBM) in the three MCS patients. TBI: traumatic brain injury*

Table 9. Neuroimaging results in the three patients.

	Brain region	*X* (mm)	*Y* (mm)	*Z* (mm)	*p* value*	*Z* value
Case 1						
PET1 < PET2	Left precuneus	-4	-56	24	0.001	4.447
	Right angular	44	-66	48	0.006	3.889
	Left angular	-40	-72	44	0.006	3.872
	Left middle occipital gyrus	-34	-92	18	0.009	3.747
	Right inferior occipital gyrus	34	-94	-2	0.020	3.329
	Right cerebellum	38	-72	-26	0.023	3.260
	Left middle frontal gyrus	-32	10	54	0.023	3.249
	Left calcarine gyrus	-6	-102	-2	0.028	3.138
	Right middle frontal gyrus	48	8	52	0.044	2.867
Case 2						
PET1 < PET2	Left temporal pole	-32	2	-18	0.000	7.222
	Left cerebellum	-46	-42	-36	0.000	4.847
	Left superior medial frontal gyrus	0	52	20	0.003	3.089
	Right thalamus	16	-14	22	0.006	2.900
VBM1 < VBM2	Left caudate	-8	10	-12	0.000	5.733
	Right caudate	23	9	18	0.001	4.669
	Left temporal fusiform gyrus	-41	-65	-12	0.001	4.115
	Left middle temporal gyrus	-63	-53	-12	0.004	3.566
	Left inferior temporal gyrus	-68	-27	-20	0.006	3.430
	Left angular gyrus	-50	-65	39	0.029	2.672
Case 3						
PET1 < PET2	Left middle frontal gyrus	-40	4	56	0.000	6.147
	Right caudate	18	-8	24	0.001	3.505
	Left caudate	-14	8	14	0.002	3.346
VBM1 < VBM2	Right thalamus	17	-7	14	0.019	3.961
	Left inferior temporal gyrus	-66	-56	-9	0.019	3.928
	Left precuneus	2	-42	59	0.019	3.901
	Left superior frontal gyrus	-11	17	63	0.019	3.792
	Right middle temporal gyrus	66	-51	-2	0.020	3.759
	Right parahippocampal gyrus	21	-4	-18	0.020	3.745
	Left superior temporal gyrus	-51	18	-30	0.020	3.718
	Left parahippocampal gyrus	-23	-24	-35	0.020	3.638
	Left precentral gyrus	-38	-4	62	0.021	3.509
	Left inferior parietal lobule	-44	-68	51	0.021	3.495
	Left parahippocampal gyrus	-24	-24	-12	0.023	3.335
	Left caudate	-17	9	15	0.024	3.240
	Right middle frontal gyrus	32	48	3	0.027	3.123

**FDR corrected*

4. Discussion

The present findings offer a new perspective to understand the neural correlates of the recovery of language-related behaviors, and more specifically command-following (behavior recovered in all three patients). We here report that the recovery of this ability in three chronic MCS patients is paralleled with an increase in brain metabolism and grey matter in regions previously related to language and/or consciousness.

First, all patients presented an increase of brain metabolism in regions that have been associated with language processing. For example, Binder et al. (2009) considered the left angular gyrus as particularly involved in semantics (i.e., sentence comprehension, complex information integration and knowledge retrieval), and this region was less hypometabolic when case 1 was MCS+ as compared to MCS-. Moreover, a recovery of its contralateral homologue was reported. According to the same authors, the left temporal areas highlighted in case 2 were also shown to be activated in language tasks and to support concept retrieval. Finally, case 3 presented a better metabolism in the left caudate, which was associated with language control skills (Crinion et al., 2006; Friederici, 2006). Using structural MRI, cases 2 and 3 also showed a larger grey matter volume in language comprehension areas (i.e., left fusiform, angular and temporal cortex) (Binder et al., 2009) when having recovered command-following. Thus our findings are congruent with previous studies in MCS patients, showing a relationship between the ability to respond to commands and left hemisphere functions (Aubinet, Murphy et al., 2018; Bruno et al., 2012). Nevertheless, we found that the structural and functional changes between MCS- and MCS+ might be bilateral. The non-dominant hemisphere could therefore contribute to the recovery of command-following. This is also consistent with previous studies showing compensatory mechanisms in the contralateral right hemisphere in AC patients (Artzi et al., 2016; Teki et al., 2013).

Furthermore, the thalamus and/or precuneus showed an improvement of metabolism in the two first patients and an increase of grey matter structure in the third case. These regions are critical for consciousness processes, and especially self-consciousness as they are part of the internal consciousness network (Di Perri et al., 2016; Vanhaudenhuyse et al., 2011). Consequently, our results tend to confirm that, besides language processing differences, MCS- and MCS+ categories might also reflect differentiated levels of consciousness at the individual level.

It is however important to note that other higher cognitive functions might be involved in the sub-categorization of the MCS. Indeed, for all three cases an improvement was shown in various frontal areas related to executive functions (Miyake et al., 2000), or in regions such as the caudate, which is implicated in learning or cognitive control (Chiu, Jiang, & Egner, 2017). These skills could also be involved in the recovery of command-following as assessed with the CRS-R.

Our results are not representative of the population and prospective studies including a large sample of patients are needed in order to overcome statistical limitations. Future longitudinal studies should also investigate the clinical implications on long-term outcomes of the transition from MCS- to MCS+, as previously suggested in Study 1. Nevertheless, our findings point-out the possibility of command-following recovery even in chronic MCS patients, which seems in line with a recovery of brain functions in the ipsi- or contra-lateral language networks, as well as in the internal consciousness network. This is particularly relevant given the importance of this behavior for a potential communication (Giacino et al., 2002; Giacino et al., 2004).

In conclusion, the reappearance of command-following in the three patients was concomitant with a recovery of metabolism and grey matter structure in language-related areas, mainly in the left temporal lobule, angular gyrus, fusiform gyrus and caudate. It was also concomitant with functional and structural recovery of structures such as the thalamus and the precuneus involved in self-consciousness. The present results indicate that the transition from MCS- to MCS+ involves recovery in networks particularly associated with both language and consciousness.

Experimental part II. Behavioral assessments of language in post-comatose patients

The lack of bedside behavioral language assessment adapted for DoC patients constitutes an important issue for speech therapists who would need more information to orientate their care. This is an even bigger issue since the presence of receptive aphasia may lead clinicians to underestimate patients' level of consciousness. This part is dedicated to the development of new evaluations, which may complement the CRS-R in order to estimate residual language abilities in post-comatose patients.

Based on the following publications:

Aubinet C, Murphy L, Bahri MA, Larroque SK, Cassol H, Annen J, Carrière M, Wannez S, Thibaut A, Laureys S, Gosseries O (2018). Brain, behavior and cognitive interplay in disorders of consciousness: A multiple case study. *Frontiers in Neurology, 9*(665).

Aubinet C, Chatelle C, Gillet S, Lejeune N, Cassol H, Laureys S, & Majerus S (*in preparation*). Validation of the Brief Evaluation of Receptive Aphasia for detection of language impairment in severely brain-injured patients.

Study 4. The Cognitive Assessment by Visual Election (CAVE)

Patients with prolonged disorders of consciousness (DoC) after severe brain injury may present residual behavioral and cognitive functions. Yet, the bedside assessment of these functions is compromised by patients' multiple impairments. Standardized behavioral scales such as the Coma Recovery Scale-Revised (CRS-R) have been developed to diagnose DoC, but there is also a need for neuropsychological measurement in these patients. The Cognitive Assessment by Visual Election (CAVE) was therefore recently created. In this study, we describe five patients in minimally conscious state (MCS) or emerging from the MCS (EMCS). Their cognitive profiles, derived from the CRS-R and CAVE, are presented alongside their neuroimaging results. Scores on the CAVE decreased along with the CRS-R total score, establishing a consistent behavioral/cognitive profile for each patient. Out of these five cases, the one with highest CRS-R and CAVE performance had the least extended cerebral hypometabolism. All patients showed structural and functional brain impairments that were consistent with their behavioral/cognitive profile as based on previous literature. For instance, the presence of visual and motor residual functions was respectively associated with a relative preservation of occipital and motor cortex/cerebellum metabolism. Moreover, residual language comprehension skills were found in the presence of preserved temporal and angular cortex metabolism. Some patients also presented structural impairment of hippocampus, suggesting the presence of memory impairments. These results suggest that brain-behavior relationships might be observed even in severely brain-injured patients and they highlight the importance of developing new tools to assess residual cognition and language in MCS and EMCS patients. Indeed, a better characterization of their cognitive and language profile will be helpful in preparation of rehabilitation programs and daily routines.

1. Aim and hypotheses

According to our systematic review, there were only a few studies attempting to behaviorally assess language at the bedside of patients with disorders of consciousness (DoC). One of them presented a new interesting test which was recently created on the grounds of clinical work: the Cognitive Assessment by Visual Election (CAVE) (Murphy, 1997, 2018). This assessment is based on the ability to understand language at a basic level and to visually fixate objects. In this fourth study, we aim to examine the behavioral and cognitive profile of different patients in minimally conscious state (MCS) and emerging from the MCS (EMCS). Performance on the Coma Recovery Scale-Revised (CRS-R) and the CAVE are compared with their neuroimaging results using fluorodeoxyglucose-positron emission tomography (FDG-PET) and voxel-based morphometry (VBM). Specifically, we hypothesized an association between patients' structural and functional brain damage and their behavioral/cognitive profile, consistent with previous studies establishing neural correlates of behavior, language and cognition.

2. Methods

a. Participants

This prospective study includes five patients who were consecutively recruited at the University Hospital of Liège. All patients completed a battery of behavioral tests including repeated Coma Recovery Scale-Revised (CRS-R) (see Study 1) and neuroimaging assessments during a one-week hospitalization, based on clinical demand. Patients with absence of visual pursuit or visual evoked potentials (as observed by an experimented ophthalmologist) were excluded, as some functional

vision is required to perform the CAVE. The control groups were the same as in Study 1. The present study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege and written informed consents, including for publication of data, were obtained from the patients' legal representatives and from the HCS.

b. Material

Cognitive Assessment by Visual Election (CAVE)

The CAVE includes 6 sub-tests to evaluate the recognition of real objects, numbers, written words, letters, pictures and colors (Murphy, 2018). Each of these sub-tests contains 10 items, with a cut-off score of 8/10 based on binomial distribution. A target object is presented simultaneously with a distractor (e.g., a pen on the left and a fork on the right visual field) and the patient is asked to look at the target (e.g., "look at the pen"). As this test requires at least the preservation of visual fixation, this tool is dedicated to MCS-, MCS+ and EMCS patients. It usually takes between 10 and 30 minutes to administer, depending on the ability to objectify patient's eye fixations and patient's fatigue. The scoring sheet is presented in appendix V (supplementary material 1). An extended version of the CAVE proposes additional subtests, including a visual memory recognition exercise that was attempted with our patients (except case 4). First, patients were presented five pictures (one at a time) and asked to memorize them. Afterward, each target was presented with a distractor and they were asked to look at the previously shown picture.

Electrophysiological measurement

A clinical standard EEG was performed using the 10-20 system (19 electrodes) and interpreted by a certified neurologist to assess the severity of the encephalopathy. Cortical activity in response to bilateral auditory, visual and nociceptive stimulations is recorded. The background rhythm and responsiveness are

assessed to determine the degree of severity of the encephalopathy and detect any potential slow or paroxystic focalization.

Neuroimaging

MRI data were acquired and preprocessed as previously described (see Study 1). The differences in grey matter volume were investigated by comparing each patient with a group of 36 HCS (see Study 1) using a parametric two-sample t-test. Both the total intracranial volume and age, centered to mean and standardized to 1, were then used as covariates. VBM results were considered significant at family wise error (FWE) corrected $p < 0.05$ at cluster level and cluster defining threshold $p < 0.001$.

A resting FDG-PET scan was performed after intravenous injection of approximately 150 MBq of FDG and preprocessed as described in Study 1. Patient data were compared to 34 HCS (see Study 1). SPM analysis identified brain regions with decreased and relatively preserved metabolism in each patient compared to HCS. The resulting set of voxel values for each contrast, constituting a statistical parametric map of the *t*-statistics (SPM{*t*}), was transformed to the unit normal distribution (SPM{Z}) and thresholded at voxel-wise $p < 0.05$ FWE-corrected and at $p < 0.001$ uncorrected.

3. Results

The main results of the five patients (all right-handed; age range: 20-66 years old; one woman) are presented in figure 12. The CRS-R and CAVE scores are presented in table 10. All VBM and FDG-PET statistical results are presented in table 10 (most significant data) and in appendix V (table S1 - supplementary material 2).

a. Case 1

This patient was admitted to our hospital 16 months after a TBI. He was diagnosed as EMCS (with a total CRS-R score of 19/23) because of his ability to functionally communicate using "yes" and "no" cards. Due to fatigue and time limitation, only four CAVE sub-tests were administered. According to the cut-off score, he was able to recognize objects, numbers, written words and letters, as well as to memorize five pictures (table 10). Overall, case 1 correctly responded to 92.5% of the administered items of the CAVE.

The clinical EEG showed abnormalities regarding the posterior and temporal derivations of the left hemisphere. As seen in table 11 and figure 12, the VBM shows grey matter damage in the left hippocampus. FDG-PET hypometabolism was observed in the left thalamus and angular gyrus ($p < 0.05$ FWE corrected), as well as the left putamen and part of the left inferior and middle temporal gyrus, the left precentral cortex and the right superior frontal cortex ($p < 0.001$ uncorrected). The most preserved metabolism was shown in the right angular gyrus ($p < 0.05$ FWE corrected) and in the right insula, middle frontal cortex, post-central cortex, rolandic operculum and superior temporal cortex ($p < 0.001$ uncorrected).

b. Case 2

Case 2 had a stroke and epilepsy due to post-surgery complications 30 months before his admission to our hospital. He was diagnosed as EMCS (with a total CRS-R score of 19/23), as he was able to functionally use objects but not to functionally communicate. Using the CAVE, the patient showed a good performance in recognizing numbers and pictures (table 10). He was just below the cut-off score with real objects and colors but he had more difficulties with discriminating letters and written words and in memorizing the pictures. Unilateral spatial neglect was suspected since his performance was better when the target item was presented on his left side. Case 2 performed well for 73% of administered items.

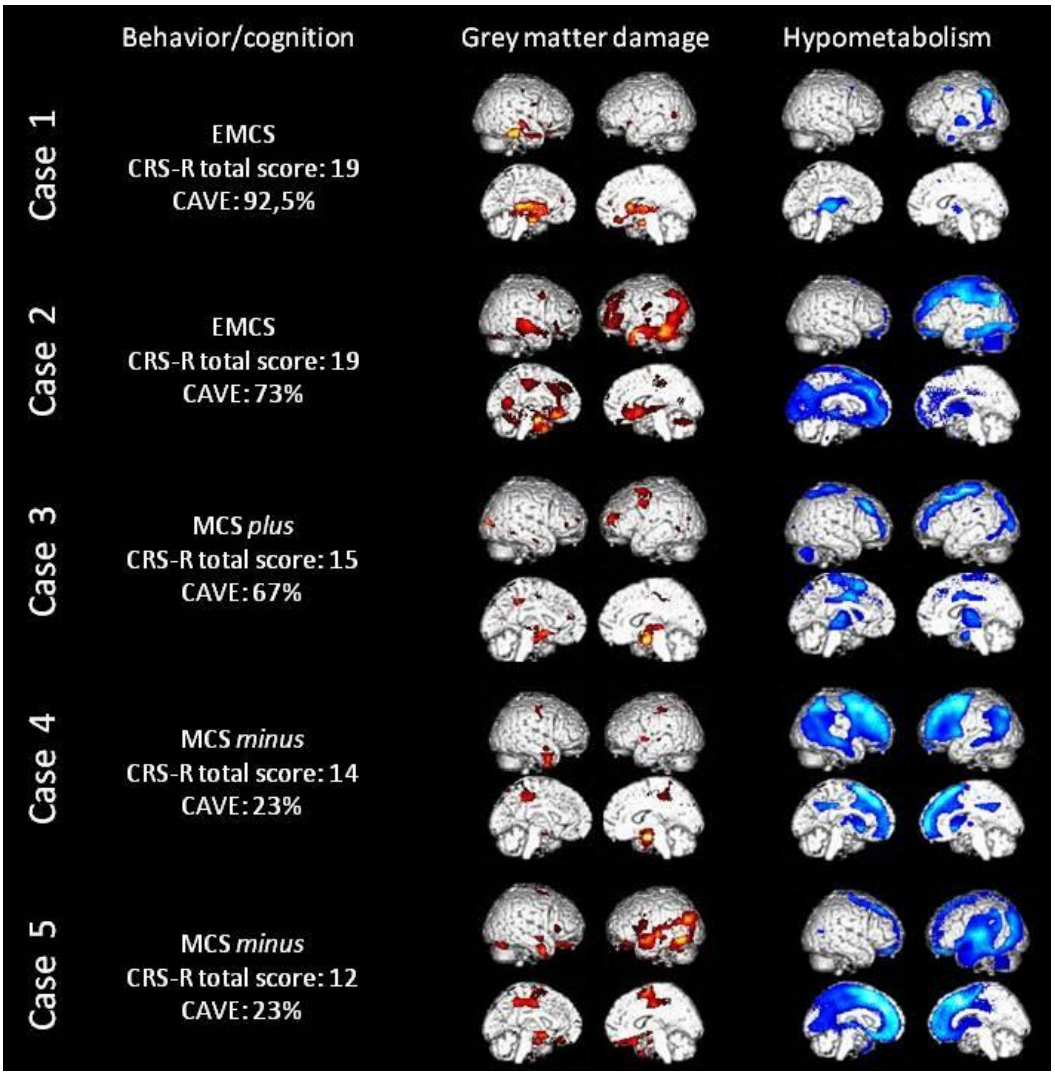

Figure 12. *Behavioral and cognitive data.. Loss of grey matter volume (2nd column in red) as assessed with VBM and cerebral hypometabolism (3rd column in blue) as assessed with FDG-PET in all five patients. Here the threshold is uncorrected 0.001 for display values. EMCS: emergence from the minimally conscious state; MCS: minimally conscious state; CRS-R: Coma Recovery Scale-Revised; CAVE: Cognitive Assessment by Visual Election.*

The clinical EEG suggests significant left hemispheric damage with a nascent encephalopathy. Neuroimaging results also show left hemisphere structural and functional damage. Significant hypotrophy in the left fusiform, left medial orbitofrontal and right superior temporal cortices was noted, as well as in the left calcarine sulcus and right cerebellum. Hypometabolism was also observed in the left

inferior parietal cortex ($p < 0.05$ FWE corrected) and in the left supplementary motor area, superior frontal cortex, cingulate cortex, precuneus, fusiform cortex, superior parietal cortex, hippocampus and amygdala, as well as bilateral rectus gyri and thalami ($p < 0.001$ uncorrected). The regions showing the most preserved metabolism were the right amygdala ($p < 0.05$ FWE corrected) and the bilateral cerebellum and right middle frontal cortex, temporal, parietal and occipital lobules ($p < 0.001$ uncorrected).

Table 10. Behavioral scores at the CRS-R and the CAVE

		CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
CRS-R	**Final diagnosis**	EMCS	EMCS	MCS+	MCS-	MCS-
	Auditory score	4*	4*	3*	2	1
	Visual score	5*	4*	3*	3*	3*
	Motor score	5*	6#	5*	5*	5*
	Oromotor/verbal score	1	2	2	2	1
	Communication score	2#	1*	0	0	0
	Arousal score	2	2	2	2	2
	Total score	19	19	15	14	12
CAVE	**Real objects**	9/10	7/10	10/10	4/10	4/10
	Numbers	9/10	9/10	8/10	NA	3/10
	Words	9/10	6/10	1/10	2/10	1/10
	Letters	10/10	5/10	7/10	NA	1/10
	Pictures	NA	10/10	9/10	NA	3/10
	Colors	NA	7/10	5/10	NA	2/10
	Percentage of success	92.5%	73%	67%	23%	23%
	Memory	5/5	3/5	1/5	NA	1/5
	Left/right differences	No	Yes	No	No	Yes

*# indicates emergence of minimally conscious state (EMCS), * indicates MCS.*
The underlined CAVE scores are below the cut-off score and thus considered as failed.
NA = not administered.

c. Case 3

This case came to our hospital 13 months after a TBI. The diagnosis was MCS+ (with a total CRS-R score of 15/23) since he was able to follow simple verbal

commands (e.g., “Look up”, “Turn your head” and “Close your eyes”). His cognition was more impaired than case 1 and qualitatively very different from case 2 (table 10). He could perform some sub-tests, namely recognizing real objects, numbers and pictures. The other attempted sub-tests (including memory) led to performance lower than the cut-off score. This patient successfully responded to 67% of presented items.

The clinical EEG was biased by abundant movement artifacts. Structural damage was shown using VBM in the bilateral hippocampi and in the right precentral cortex. Analysis of FDG-PET data showed significant hypometabolism in bilateral precentral cortex, right middle frontal cortex and left middle occipital cortex ($p < 0.05$ FWE corrected), as well as in the left inferior occipital cortex, middle frontal gyrus and supplementary motor area and bilateral middle cingulate cortex and thalami ($p < 0.001$ uncorrected). The most preserved metabolism was observed in the left supramarginal gyrus ($p < 0.05$ FWE corrected) and the right inferior frontal, inferior parietal, angular and superior temporal cortex, as well as left inferior frontal, middle and superior temporal cortex ($p < 0.001$ uncorrected).

Table 11. Regions showing significant grey matter hypotrophy, impaired and preserved metabolism.

	Brain regions	*p*(FWE-corr)	*T*	*x*	*y*	*z*
GREY MATTER						
Case 1 < HCS	L hippocampus	0	6,4	-30	-15	-17
Case 2 < HCS	L fusiform cortex	0	11,5	-29	-15	-24
	L medial orbitofrontal cortex	0	8,1	-8	27	-12
	R superior temporal cortex	0,002	6,1	68	-9	-9
	L calcarine	0,035	4,9	-11	-60	11
	R cerebellum	0,038	4,3	23	-77	-30
Case 3 < HCS	R hippocampus	0,004	5,9	20	-6	-20
	L precentral cortex	0,025	4,7	-27	-4	53
	L hippocampus	0,036	4,7	-15	-6	-12
Case 4 < HCS	R amygdala	0	6,5	30	-4	-20
Case 5 < HCS	L inferior temporal cortex	0	8,0	-53	-69	-9
	R supplementary motor area	0,001	5,2	11	-1	65

HYPOMETABOLISM						
Case 1 < HCS	L angular gyrus	0,016	5,3	-46	-70	38
	L thalamus	0,015	5,2	-8	-18	6
Case 2 < HCS	L inferior parietal	0	15,6	-54	-26	36
Case 3 < HCS	L precentral cortex	0	12,2	-28	-18	68
	R middle frontal cortex	0,003	9,2	34	34	38
	R precentral cortex	0,012	6,0	26	-28	70
	L middle occipital cortex	0,006	5,6	-32	-90	8
	Brain stem	0,002	5,5	2	-24	-4
Case 4 < HCS	R middle frontal cortex	0	8,5	44	10	50
	L caudate	0,013	7,1	-16	12	8
	L middle temporal cortex	0	6,5	-50	-68	18
	R middle cingulate cortex	0,02	4,7	4	-50	34
Case 5 < HCS	L middle temporal cortex	0	15,4	-54	-58	20
PRESERVED METABOLISM						
Case 1 > HCS	R frontal lobe (white matter)	0	7,2	26	24	24
	R angular gyrus	0,041	4,5	48	-48	32
Case 2 > HCS	R amygdala	0	13,1	34	2	-24
Case 3 > HCS	R frontal lobe (white matter)	0	9,1	46	-2	18
	L supramarginal gryus	0	9,1	-50	-28	30
Case 4 > HCS	L insula	0	10,0	-30	-8	18
	R insula	0,006	9,8	32	-4	18
	R cerebellum	0	7,0	20	-56	-20
Case 5 > HCS	R amygdala	0	17,3	34	0	-28

L = left; R = right, HCS = healthy control subjects.

d. Case 4

Case 4 sustained a hypoxic-ischemic brain injury following an insulin overdose; she was 3 years post-hypoglycemia. This patient showed the requested visual functions, as well as automatic oriented motor reactions, therefore she was considered as being in a MCS- with a CRS-R total score of 14/23. Nevertheless, she was an atypical MCS- patient due to her ability to walk when guided by someone else. Using the CAVE, she failed to recognize real objects, numbers, words and colors. The remaining subtests (i.e. letters and pictures recognition) were not

administered due to patient fatigue. Case 4 performed well for 23% of the administered items.

Despite the presence of muscular artifacts, the clinical EEG showed significant encephalopathy with no sign of lateralization. The neuroimaging data showed hypotrophy of the right amygdala. Moreover, hypometabolism was mainly found in the right middle frontal and cingulate cortex and in the left caudate and middle temporal cortex ($p < 0.05$ FWE corrected), as well as in bilateral angular gyrus, caudate, putamen, thalami and frontal cortex, in the right middle temporal and inferior parietal cortex, in the left insula and middle temporal cortex ($p < 0.001$ uncorrected). On the contrary, the most preserved metabolism was shown in the right cerebellum ($p < 0.05$ FWE corrected), in the bilateral insula and putamen, and in the left cerebellum, precuneus, paracentral and postcentral cortex ($p < 0.001$ uncorrected).

e. Case 5

This last patient had a stroke 13 months before his stay in our hospital. He was diagnosed as MCS- with a CRS-R total score of 12/23. He did not show any residual language ability but he was able to visually fixate and track objects, as well as to automatically open his mouth when a spoon was moved towards it (i.e., automatic motor response). Similarly to case 4, this patient failed to recognize (and memorize) the visual targets, despite his high arousal enabling us to attempt all CAVE subtests. As for case 4, case 5 visually fixed the target item for 23% of the trials but left/right differences were observed.

The clinical EEG showed a symmetrical slow dysrythmia with no paroxysm, suggesting a slow diffuse brain damage with no irritating nature. Grey matter hypotrophy was shown in the left inferior temporal cortex and right supplementary motor area. The FDG-PET results show the presence of significant hypometabolism in the left middle temporal cortex ($p < 0.05$ FWE corrected), the bilateral superior frontal and cingulate cortex, the left thalamus, precuneus, and parietal cortex ($p <$

0.001 uncorrected). Preserved metabolism in the right amygdala was observed (p < 0.05 FWE corrected), as well as in the vermis, the bilateral cerebellum, the left hippocampus and the right parieto-occipito-temporal regions including the right precuneus and angular gyrus (p < 0.001 uncorrected).

4. Discussion

In this study, patients in MCS or EMCS have been assessed with a broad spectrum of (para)clinical tools. Using the CAVE, it has been possible to evaluate the cognitive profile of severely brain-injured patients, and the importance of the use of such new bedside neuropsychological assessments is highlighted. It was hypothesized that CAVE profiles would correspond to patients' cerebral structure and brain activity. Comparing all patients, the highest scorer on bedside behavioral and language-based cognitive assessments (i.e., case 1) showed less extended levels of cerebral hypometabolism. It was also found that the percentage of success on the CAVE decreased along with the CRS-R total score (see table 10), establishing a consistent behavioral/cognitive profile for each patient. The cognitive profile obtained from the CRS-R and the CAVE was mostly found to correspond to structural and functional results. As shown in figure 12, both neuroimaging techniques also seem in agreement: grey matter damages are generally paralleled with hypometabolism of the same structures, and this hypometabolism is even more widespread. Below, we discuss cognitive functions in different domains and compare the behavioral results with neuroimaging findings.

Visual functions

All patients were able to visually fixate and pursuit objects and all showed a relative structural and metabolic preservation of occipital lobule. Regarding case 1, the ability to visually fixate objects and the use of a visually-based communication code were consistent with the absence of significant hypometabolism and grey

matter hypotrophy in the occipital cortex. The difficulty to perform well with letters, words and colors in case 3 may be consistent with the apparent hypometabolism within the left occipital cortex (Bartels & Zeki, 2000; Garrett et al., 2000; James et al., 2005; Koyama et al., 2010). In addition, number recognition appeared intact in this patient. This ability has been shown to rely on the right lateral occipital area (Park et al., 2012), and our patient showed no significant hypometabolism in this area. Hence, our findings suggest a dissociation between letter and number recognition which was associated with specific occipital lesions. Both MCS- patients were unable to successfully recognize the CAVE target items. Despite their ability to visually fixate one object when it was presented alone, none of these two patients showed responses to command, which suggest that they did not understand the task instructions (see next section).

Unilateral spatial neglect and/or hemianopia were suspected in case 2 and case 5 since there was a significant difference in the performance between left and right CAVE target items. Indeed, a deviation of their eyes toward their left side was noted in both patients. Karnath & Rorden (2012) have highlighted the role of a perisylvian network in spatial neglect, including the temporo-parietal junction, the temporal lobules and underlying insula, as well as the ventro-lateral prefrontal cortex. Accordingly, these two patients showed hypometabolism and hypotrophy of grey matter in some of these cerebral regions.

Language and executive functions

Case 1 was the only patient who could functionally communicate using a "yes/no" code. This ability requires language and executive functions such as mental flexibility. Hence recovery of communication does not seem surprising due to the preserved metabolism and absence of grey matter damage in frontal lobules (Badre & Nee, 2017; Munro et al., 2017). Besides communication, this patient was also able to follow simple commands and to understand the 'look at' commands during the administration of the CAVE. Nevertheless, the EEG and FDG-PET analysis reported abnormalities regarding the posterior and temporal derivations of the left hemisphere, shown to be dedicated to semantics (Binder et al., 2009). Specifically,

we found peaks of hypometabolism within the left angular gyrus, which was related to sentence comprehension (Binder et al., 2009; Dronkers et al., 2004; Friederici et al., 2003). Still, this patient's residual language skills may emerge from neural plasticity using the cerebral areas that are either around the lesion, or in the contralateral cerebral regions (Artzi et al., 2016; Heiss et al., 1999; Heiss & Thiel, 2006; Teki et al., 2013; Vitali et al., 2007). Indeed, right angular gyrus and superior temporal cortex showed preserved metabolism.

In contrast, case 2 was unable to functionally communicate and read written letters and words during the CAVE assessment. This was consistent with the massive left cerebral lesion that was detected with VBM, FDG-PET and clinical EEG (Binder et al., 2009; Dronkers, Ivanova, & Baldo, 2017). More precisely, this patient showed hypometabolism and grey matter reduction in the left fusiform cortex, known to be the "visual word form area" (Carreiras et al., 2014; Dronkers et al., 2017; Friederici et al., 2003). Therefore, these data matched well with his inability to recognize letters and words. Taken together, the CAVE results suggested that the more linguistic were the items, the more difficult it was for this patient to answer. Thus, it is likely that this patient had severe aphasic difficulties. Nevertheless, he was systematically able to follow (and thus understand) commands. This may correspond with the absence of hypometabolism in areas such as the left superior temporal cortex (Binder et al., 2009). In addition, similarly to case 1 it could be argued that he recovered such abilities by means of neural plasticity (i.e., contralateral compensation).

Case 3 was able to understand and follow commands and he could recognize objects, pictures and numbers. All these skills require residual language comprehension and relative preservation of semantic processing, which is related to left temporal areas (Binder et al., 2009). Accordingly, we observed the absence of grey matter hypotrophy and the presence of preserved metabolism regarding the left temporal lobule. Again, this patient showed an inability to recognize letters and written words. If this patient, contrary to case 2, did not show impairment of the left fusiform gyrus (i.e., the visual word form area), he still showed hypometabolism in

regions that are very close (i.e., the left inferior and middle occipital cortex). These findings were also consistent with the patient's inability to discriminate different colors (Bartels & Zeki, 2000; Lafer-Sousa, Conway, & Kanwisher, 2016).

The inability of cases 4 and 5 to show language-based signs of consciousness (i.e., command-following, intelligible verbalization and communication) and to recognize CAVE items corresponded to their hypometabolism, notably regarding the left angular gyrus (Binder et al., 2009). These results implied a lack of verbal comprehension due to accumulated language and cognitive impairments. Indeed, more impaired language functions in MCS- than in MCS+ patients was suggested by previous studies (Aubinet, Larroque et al., 2018; Bruno et al., 2012).

Motor functions

Repeated assessments on the CRS-R did not demonstrate functional use of objects in case 1 but it was noted that this patient tended to grab his bed sheets and try to reach objects. Accordingly, we did not observe hypometabolism within the motor cerebral areas (figure 12). Furthermore, case 2's ability to functionally use some objects (i.e., a comb) could emerge from preserved right motor areas. Our third and fifth cases obtained the same motor subscale score at the CRS-R as case 1 since they showed automatic oriented movements with their mouth. The inability to move their limbs could thus be related to case 3's hypometabolism of the precentral cortex and supplementary motor area and to case 5's damage of the right supplementary motor area. Interestingly, case 4 was an atypical MCS- patient because she was able to walk despite her inability to respond to commands. This capacity was probably possible because of preserved metabolism of the left paracentral and postcentral sensorimotor cortex (Pizzamiglio et al., 2017; Seeber et al., 2015; Wagner et al., 2014). In addition, this patient also showed a preserved cerebellum and previous studies have highlighted its role in gait and movement coordination (Buckley, Mazzà, & McNeill, 2017).

Memory and consciousness

Case 1 performed perfectly to the memory subtest. Nevertheless, it is a recognition task and other higher order memory processes might still be impaired. Indeed, case 1 (as well as case 3) showed impaired grey matter structure in the hippocampus, which has shown to be related to episodic memory in numerous previous studies (e.g., Poldrack and Packard, 2003; Ranganath, 2010). Since memory difficulties were presented on this subtest by the other cases, one could thus hypothesize the presence of memory impairment in all five patients.

All patients were no less than minimally conscious, and at least part of the external FPN was preserved in all of them (Laureys et al., 1999). Interestingly, in our atypical case 4 the metabolism of this external network seemed less preserved than the other cases. The internal DMN was probably slightly more affected than the external network in our patients. For instance, the left precuneus was shown to be hypometabolic in case 2 and case 5, whereas the thalamus (known to play an important role in consciousness; Crone et al., 2013) was hypometabolic in all five patients. Since thalamo-cortical alterations were found in other brain-injured patients with chronic fatigue problems (Berginström et al., 2017), case 1's fatigue might also be at least partially explained by the left thalamus functional impairment.

Limitations

This multiple case report only provides preliminary findings; more patients are needed in order to overcome statistical limitations and confirm the relationships between cognition and brain structure and function at the group level. The heterogeneity of DoC patients makes this research very challenging. Additionally, even if all five patients had good premorbid English skills, they were all native Dutch-speaking, which could have introduced some biases regarding the CAVE assessment. Moreover, the performance at the CAVE is multi-determined, requiring visual functions, language comprehension and other subtest-specific abilities such as reading. As such, the CAVE might help us to detect the presence of aphasia in our patients, but it does not discriminate or specify which language functions are altered

(e.g., phonology *versus* semantics). New material could be included to evaluate MCS and EMCS patients' cognitive functions in a more specific way. Finally, the CAVE seems to be useful only for patients who are at least MCS+.

In conclusion, the performance of all patients using the CRS-R and the CAVE was consistent, and it mostly corresponded to their brain structure and metabolism in line with previous research on patients with focal cerebral lesions. For instance, residual language comprehension skills were found in the presence of preserved temporal and angular cortex metabolism. Our results suggest that brain-behavior relationships might be observed even in severely brain-injured patients. This research further highlights the importance of the development of behavioral assessment tools, such as the CAVE, both to inform clinical practice and for scientific interest. Clinically, besides the CRS-R this new test allows to refine the patient's cognitive profile. This knowledge will be helpful in preparation of rehabilitation programs and daily routines. Such information may be important also for the investigation of the neural correlates of behavior and cognition in patients with severe brain injury.

Study 5. The Brief Evaluation of Receptive Aphasia

The presence of language deficits may lead to an underestimation of consciousness level in brain-injured patients. At the same time, the assessment of language in patients with disorders of consciousness (DoC) is prevented by their limited behavioral responses. We here present a new language comprehension assessment tool based on visual fixation of images for DoC patients. The Brief Evaluation of Receptive Aphasia (BERA) assesses receptive phonological, semantic and morphosyntactic abilities. The BERA as well as the Language Screening Test (LAST) were first administered to 52 aphasic conscious patients on two consecutive days in order to determine its validity and reliability. Next, this new tool was administered to 4 post-comatose patients, who were also examined by means of the Coma Recovery Scale-Revised (CRS-R), positron emission tomography and structural magnetic resonance imaging. In aphasic conscious patients, the BERA showed satisfactory intra- and inter-rater reliability, internal and concurrent validity with the Language Screening Test. In DoC patients, the BERA scores suggested the presence of selective receptive difficulties for phonological, semantic and particularly morphosyntactic abilities. These results were in line with their functional and structural neuroimaging data. The BERA may complement the widely used CRS-R when assessing and diagnosing DoC patients by providing a more systematic and detailed characterization of language abilities in these severely brain-injured patients.

1. Aim and hypotheses

The Cognitive Assessment by Visual Election (CAVE) would be a reliable tool to detect residual cognition in patients with disorders of consciousness (DoC). Nevertheless, this tool does not distinguish various domains of language nor include any control of psycholinguistic variables. Speech therapists would thus need more information to establish language profiles in this population.

Our fifth study consequently presents the development and validation of the "Brief Evaluation of Receptive Aphasia" (BERA). This assessment tool aims to better identify language impairment in DoC patients, by examining in a specific manner phonological, semantic and morphosyntactic receptive abilities, which can be differentially affected in classical aphasia syndromes (Ardila, 2010).

We first performed the BERA assessment in healthy control subjects (HCS), expecting a ceiling effect in all of them. Second, aphasic conscious (AC) patients were assessed using the BERA and the Language Screening Test (LAST) (Flamand-Roze et al., 2011) on two consecutive days and by three blind examiners, in order to determine intra- and inter-rater reliability, as well as internal and concurrent validity (i.e., sensitivity to language impairment). Third, the BERA tool was administered to post-comatose patients with severe brain injury, along with repeated Coma Recovery Scale-Revised (CRS-R), fluorodeoxyglucose-positron emission tomography (FDG-PET) and structural magnetic resonance imaging (MRI).

As previous studies recommended the use of multimodal assessments (Majerus et al., 2009), we hypothesize that the presence of language impairment could be documented by combining the BERA and CRS-R assessments with measurement of brain glucose metabolism and grey matter structure.

2. Methods

a. Participants

We first recruited a convenience sample of 10 HCS (i.e., age range 21-79 years old, 4 women, 5 low [scored 10] and 5 high [scored 2] socio-economic statuses according to the European Socio-Economic Classification; Rose & Harrison, 2007) to ensure that they could all reach the maximum BERA score.

Fifty-two AC patients were recruited in several rehabilitation centers with the following inclusion criteria: (1) French-speaking adults (> 18 years); (2) brain injury resulting from a stroke, TBI, anoxia, cortical edema or hypoglycemia/ethylism; (3) language impairment as assessed by an experienced speech and language therapist; and (4) time since onset exceeding three weeks to avoid confusion. Exclusion criteria were: (1) presence of blindness or any other visual deficit without correction; (2) presence of deafness or any other auditory deficit without correction; (3) impairment of vigilance or confusion according to the medical staff.

Furthermore, 4 MCS/EMCS patients were recruited in the University Hospital of Liege, according to the following criteria: (1) French-speaking adults (> 18 years); (2) a diagnosis of chronic (> 1 month) MCS/EMCS as based on repeated CRS-R assessments (Wannez, Heine, et al., 2017); (3) severe brain injury and period of coma (all TBI); (4) preserved visual fixation and pursuit as assessed with the CRS-R. The exclusion criteria were similar to those for AC patients but we additionally excluded patients on the basis of unfavorable clinical context (e.g., respiratory congestion).

Individual demographic data of all participants are reported in table 12. Again, the study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege and written informed consent was obtained from the patients or their legal representatives as well as from the HCS.

b. Material

Brief Evaluation of Receptive Aphasia (BERA)

The BERA involves the visual selection of one image out of two possible choices. This mode of presentation and response was chosen since reproducible visual fixation and pursuit have been shown to be the most robust behaviors in a group of 282 MCS patients (Wannez, Gosseries, et al., 2017). The two images for each item were presented at about 40 centimeters of the patient's face with a between-picture horizontal distance of 30 centimeters. In case of suspected spatial neglect, the images were presented in a vertical arrangement. The examiner first asked the patient to look at both images, and then pronounced a word or a sentence and encouraged the patient to fixate only the target-image. The material of the BERA was developed for use in French-speaking patients.

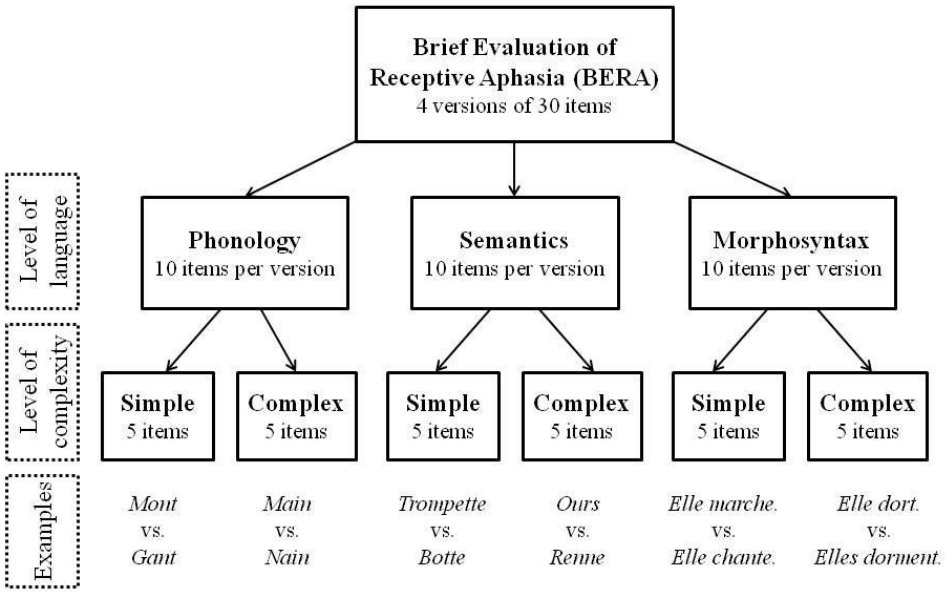

Figure 13. *Repartition of items within the BERA.*

We elaborated 4 parallel versions of the BERA, each containing a total of 30 items assessing phonological, semantic and morphosyntactic language domains

(figure 13 and appendix VI). For each language domain, half of the items (i.e., 5 items) were considered as "simple" since the distractor was unrelated to the target (e.g., *mont* [mount] versus *gant* [glove], *trompette* [trumpet] versus *botte* [boot] or *Elle marche* [She walks] versus *Elle chante* [She sings]), while the other half of the items was labelled as "complex" as they shared phonemes, semantic category or morphosyntactic elements with the target (e.g., *main* [hand] versus *nain* [dwarf], *ours* [bear] versus *renne* [reindeer] or *Elle dort* [She sleeps] versus *Elles dorment* [They sleep]). The phonological items were thus composed of pairs of monosyllabic words, which either shared a single phoneme or not. The semantic items had been adapted from "Lexis" test battery (de Partz et al., 2001) and were composed of pairs of frequent words that were either from different semantic categories or from the same semantic category. The morphosyntactic items were short sentences inspired from the Montréal-Toulouse protocol (Joanette, Nespoulous, & Lecours, 1998). They varied either with regard to their meaning (i.e., same grammatical construction for the two sentences), or with regard to their grammatical structure.

Each BERA version proposed an equal number of left and right target presentations and a randomized order of items. The examiner scored 1 point if the patient fixated the target-image, 0 in case of error or absence of fixation. Several scores were calculated: total score (out of 30 for each version), score for left-sided or right-sided items (out of 15), phonological/semantic/morphosyntactic scores (out of 10) and simple or complex phonological/semantic/morphosyntactic scores (out of 5).

Language Screening Test (LAST)

The LAST (Flamand-Roze et al., 2011) was administered to AC patients only and allowed to assess concurrent validity of the BERA. This test had been designed to detect language impairment in acute stroke patients and is composed of two parallel versions of 5 subtests (naming, repetition, automatic speech, picture recognition and verbal instructions) and a total of 15 items (i.e., 8 language production items and 7 comprehension items) for each version.

Table 12. Individual demographical data and BERA scores in the aphasic conscious patients.

Patient	Age	Gender	Etiology	Days post-onset	Brain lesion	Aphasia type	BERA phono-logy	BERA seman-tics	BERA morpho -syntax	BERA total score	Duration (minutes)
AC1	45	Male	Stroke	26	Left perisylvian area*	Non-fluent	10	10	10	30	6
AC2	61	Female	Cortical edema	77	Left parieto-temporal cortex*	Fluent	10	10	10	30	6
AC3	48	Male	Stroke	37	Left perisylvian area*	Fluent	6	7	8	21	5
AC4	46	Female	Stroke	126	Extended bilateral cortex*	Global	9	8	8	25	10
AC5	64	Female	Stroke	44	Left fronto-temporal cortex	Non-fluent	8	7	6	21	12
AC6	68	Male	Stroke	41	Left fronto-parietal cortex	Non-fluent	10	10	8	28	5
AC7	17	Female	Anoxia	137	Bilateral perivylsvian areas*	Non-fluent	7	10	10	27	10
AC8	54	Female	Stroke	128	Left fronto-temporo-parietal cortex*	Global	8	10	8	26	8
AC9	78	Female	Stroke	22	Left perisylvian area*	Non-fluent	10	10	9	29	4
AC10	85	Female	Stroke	52	Left capsular area*	Global	9	9	8	26	13
AC11	48	Male	TBI	179	Right subdural area	Fluent	9	9	5	23	8
AC12	63	Male	Stroke	81	Left parietal cortex*	Conduction	10	10	10	30	5
AC13	75	Male	Stroke	78	Left perisylvian area*	Non-fluent	5	6	6	17	6
AC14	68	Male	Stroke	44	Left perisylvian area*	Conduction	10	8	9	27	6
AC15	30	Female	Stroke	163	Left fronto-temporo-insular cortex	Mixt	10	10	10	30	4
AC16	79	Female	TBI	61	Right temporo-parieto-occipital cortex	Non-fluent	7	9	9	25	6
AC17	66	Male	TBI	123	Left temporal cortex	Mixt	9	10	7	26	10
AC18	78	Male	Stroke	69	Left perisylvian area*	Mixt	7	8	7	22	7

AC19	80	Female	Stroke	37	Left temporal cortex	Fluent	7	8	8	23	5
AC20	65	Male	Stroke	80	Left perisylvian area*	Global	8	10	6	24	7
AC21	83	Male	Stroke	58	Left hemisphere	Non-fluent	9	9	10	28	10
AC22	68	Female	Stroke	125	Left perisylvian area*	Fluent	7	6	2	15	9
AC23	67	Male	Stroke	101	Left perisylvian area*	Non-fluent	8	8	9	25	6
AC24	52	Male	Stroke	547	Left perisylvian area*	Mixt	9	10	9	28	3
AC25	68	Female	Stroke	91	Left hemisphere	Mixt	10	10	9	29	6
AC26	29	Male	Stroke	543	Left perisylvian area*	Non-fluent	9	10	9	28	4
AC27	57	Male	Stroke	93	Left capsulo-lenticular cortex	Fluent	7	9	10	26	10
AC28	87	Female	Stroke	49	Left fronto-parietal cortex	Non-fluent	9	10	9	28	5
AC29	50	Female	Stroke	152	Left perisylvian area*	Non-fluent	9	8	8	25	5
AC30	56	Male	Stroke	85	Left hemisphere	Non-fluent	9	10	9	28	6
AC31	56	Male	Stroke	105	Left perisylvian area*	Fluent	10	10	10	30	3
AC32	80	Female	Stroke	130	Left perisylvian area*	Non-fluent	7	8	7	22	9
AC33	64	Female	Stroke	86	Left occipito-temporal cortex*	Fluent	10	9	9	28	5
AC34	54	Female	Hypoglycemia/ethilysm	64	Left hemisphere	Transcortical motor	6	8	5	19	4
AC35	89	Female	Stroke	120	Left perisylvian area*	Non-fluent	8	6	6	20	9
AC36	67	Male	Stroke	50	Bilateral perivylsvian areas*	Non-fluent	10	10	9	29	4
AC37	82	Female	Stroke	59	Left perisylvian area*	Non-fluent	9	10	9	28	5
AC38	45	Female	Stroke	350	Right perisylvian area	Non-fluent	8	10	7	25	3
AC39	44	Male	Stroke	174	Right perisylvian area	Non-fluent	10	10	10	30	4
AC40	69	Male	Stroke	57	Left perisylvian area*	Non-fluent	9	9	10	28	4

AC41	59	Male	TBI	120	Left temporal cortex	Fluent	10	10	7	27	5
AC42	78	Male	Stroke	45	Left parieto-occipital cortex*	Non-fluent	8	10	9	27	5
AC43	87	Male	Stroke	58	Left hemisphere	Non-fluent	10	10	10	30	5
AC44	42	Male	TBI	207	Left parieto-temporal cortex*	Non-fluent	10	10	10	30	4
AC45	62	Female	TBI	90	Left temporal cortex	Non-fluent	10	10	9	29	4
AC46	67	Male	Stroke	49	Left hemisphere	Mixt	6	10	8	24	7
AC47	72	Female	Stroke	43	Left perisylvian area*	Non-fluent	7	8	10	25	7
AC48	84	Female	Stroke	37	Left perisylvian area*	Global	8	9	9	26	3
AC49	79	Male	Stroke	14	Left parietal cortex*	Non-fluent	10	9	10	29	4
AC50	84	Female	Stroke	58	Left perisylvian area*	Non-fluent	7	8	9	24	9
AC51	77	Female	Stroke	19	Left temporo-occipital cortex*	Transcortical motor	10	9	9	28	5
AC52	84	Female	Stroke	34	Left capsulo-lenticular cortex	Conduction	10	10	10	30	5
						Mean	8.615	9.077	8.423	26.115	6.154
						Standard-deviation	1.189	0.958	1.287	2.76	1.938
						Minimum	5	6	2	14	3
						Maximum	10	10	10	30	13
DoC1	40	Male	TBI	750			8	8	**5**	**21**	17
DoC2	30	Male	TBI	2340			7	8	7	22	5
DoC3	63	Male	TBI	150			8	**6**	**2**	**16**	20
DoC4	34	Male	TBI	150			7	**6**	**3**	**16**	15

**Posterior lesions of the left hemisphere. The BERA scores of patients with disorders of consciousness (DoC) which are presented in bold type are significantly lower than the group of aphasic conscious (AC) patients. TBI: traumatic brain injury.*

Neuroimaging

FDG-PET data were acquired and preprocessed as previously described in Study 1. Structural MRI data were obtained with a T1-weighted 3D gradient echo sequence on a 3T MRI scanner (Siemens Magnetom Vida). A T1 voxel-based morphometry (VBM) analysis (Ashburner & Friston, 2000) was carried out with the CAT12 toolbox, with non-linear warping and modulation of the grey matter to ensure the preservation of the volumes after the normalization step, and a DARTEL (Ashburner, 2007) template as described in Study 1.

c. General procedure

The items of all four versions of the BERA had been at first administered to the HCS in order to check that all of them could reach a BERA score of 30/30. They were asked to perform the four versions and give their opinion about the material. This step also aimed to ensure that the images used in the BERA provided an accurate representation of the word/sentence to which they were associated.

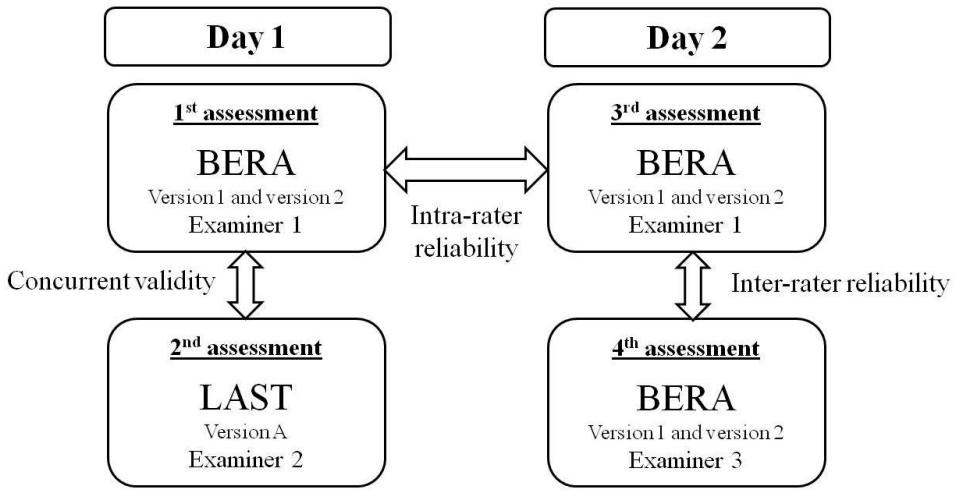

Figure 14. *Example of assessment procedure for AC patients, using one Language Screening Test (LAST) and multiple Brief Evaluation of Receptive Aphasia (BERA).*

All AC patients were assessed by three different speech therapists using either the BERA (three evaluations) or the LAST (one evaluation). Each examiner remained blind regarding the scores obtained by the two other examiners. The evaluations were performed on two consecutive days as illustrated in figure 14. The order of administration and the examiner (1, 2 or 3) were randomized across the sample of AC patients. In order to avoid fatigue effects in the AC patients, two out of the four versions of the BERA were randomly chosen to be administered to each of them, as well as one of the two versions of the LAST. For example, in patient 1 the LAST (i.e., version A) was administered together with the BERA (i.e., versions 1 and 2) on day 1, and the BERA (i.e., again versions 1 and 2) was performed twice on day 2 (figure 14). Each assessment was separated by a break of 40 to 100 minutes, again to avoid fatigue effects.

In line with the previous studies, MCS and EMCS patients were behaviorally assessed using repeated CRS-R (i.e., at least five evaluations as recently recommended; Wannez, Heine et al., 2017) during a one-week hospitalization. One version of the BERA was administered by two examiners in order to score the response based on both opinions. This consensus allowed them to objectify the visual selection of images as accurately as possible. Indeed, the scoring of visual responses in DoC patients is complicated by the common presence of motor and visual difficulties, whereas the AC patients were generally able to move the hand and point to the target. Finally, the CRS-R was daily administered (including after the BERA and prior to the neuroimaging assessments), and the patients underwent the structural MRI scan two days prior to BERA assessment, and the FDG-PET scan one day after BERA assessment.

d. Statistical analyses

Several psychometric variables of the BERA were examined in the AC sample. Internal consistency was assessed via Spearman correlations between the scores of the four different versions of the BERA. As only two versions of the BERA could be

administered by patient, only a few assessments could here be compared (e.g., only 9 patients performed both versions 1 and 2, leading to low D*f*). Wilcoxon tests were used to ensure the absence of significant differences between left versus right presentation of items, and the presence of significant differences between simple versus complex items. Moreover, concurrent validity (i.e., comparison between the LAST and BERA scores) and intra-rater reliability (i.e., comparison between the two BERA assessments performed by the same examiner on the two consecutive days) were analyzed using Spearman correlations, whereas inter-rater reliability was examined using intra-class correlations (Cronbach's alpha). Chi-squared tests were used to check for differences in the proportion of AC patients presenting phonological, semantic or morphosyntactic deficits (i.e., at least one error).

The BERA scores and sub-scores obtained in MCS and EMCS patients were compared to the mean scores obtained by the AC patients using Crawford and Howell's modified t-tests (Crawford, Howell, & Garthwaite, 1998). Results that were similar to those obtained in AC patients would suggest the presence of language comprehension difficulties, due to the presence of aphasia and/or other associated cognitive deficits. Differences between left versus right presentation of items (i.e., allowing the detection of spatial neglect) and simple versus complex items (i.e., highlighting complexity effects) were analyzed at the individual level using Chi-squared tests.

For assessing brain metabolism, the standard uptake value (SUV) for each patient was visually inspected and compared to HCS (n = 34, as in Study 1). Concerning MRI data, a VBM analysis compared each patient to another sample of HCS (n = 10, age range 23-46 years, 6 women). SPM analyses identified brain regions showing decreased or relatively preserved metabolism or reduced grey matter volume in each patient compared to the corresponding control group. For both analyses (i.e., FDG-PET and VBM), two-sample t-tests were performed to compare each patient to the control group, and the results were considered significant at $p < 0.05$ corrected for false discovery rate (FDR).

3. Results

a. Psychometric characteristics of the BERA assessment tool in AC patients

The BERA scores (i.e., at the first administration regardless of the version) of AC patients are reported in table 12.

Internal consistency and validity

We observed moderate to strong correlations (Akoglu, 2018) between the four versions of the BERA administered to the AC group: version 1 and 2 (r = 0,858 ; p = 0,003; Df = 7), version 1 and 3 (r = 0,945 ; p < 0,001; Df = 6), version 1 and 4 (r = 0,677 ; p = 0,045; Df = 6), version 2 and 3 (r = 0,833 ; p = 0,020; Df = 5), version 2 and 4 (r = 0,935 ; p < 0,001; Df = 8) and version 3 and 4 (r = 0,670; p = 0,049; Df = 8). Note that the correlation coefficients between versions 1 and 4 and between versions 3 and 4 were however lower than 0,8.

As expected, Wilcoxon tests showed a difference between complex and simple items (W = 835; p < 0,001; Df = 96,957), suggesting increased task difficulty for complex items. Also as expected, there was no significant difference between left and right presentation of items (W = 1223; p = 0,392; Df = 94,04).

Concurrent validity

The concurrent validity analysis also showed moderate to strong correlations between the LAST total score and the score of the first administered BERA (r = 0,667; p < 0,001; Df = 50), the LAST total score and the second administered BERA (r = 0,658; p < 0,001; Df = 50), the LAST comprehension sub-score and the first administered BERA (r = 0,586; p < 0,001; Df = 50), as well as the LAST comprehension sub-score and the second administered BERA (r = 0,729; p < 0,001; Df = 50).

Intra- and inter-rater reliability

The comparison of BERA scores that were obtained by the same examiner on the two consecutive days led to a strong correlation (r = 0,826; p < 0,001; Df = 50). The intra-class correlation coefficient between both BERA assessments of the same day (i.e., administered by two different examiners) showed an excellent inter-rater reliability (α = 0,919; Df = 50) (Koo & Li, 2016).

Estimation of individual performance profiles

At individual level, 32/52 patients notably showed a posterior lesion of the left hemisphere, which is more prone to cause comprehension impairment. Among this sub-sample, the BERA allowed to reveal the presence of receptive language difficulties (i.e., at least one error) in 27/32 patients (i.e., 84%).

Next we assessed the extent to which the different subscales of the BERA were able to highlight specific language deficits as a function of phonological, semantic and morphosyntactic domains. Given that healthy control subjects presented 100% accurate performance on all subscales, we considered the presence of a deficit in a specific domain when at least one item was incorrect. By doing this, we observed that 8/52 patients had no deficit, 33/52 patients presented phonological impairment, 25/52 semantic impairment and 37/52 morphosyntactic impairment. This proportion of patients with morphosyntactic impairment was significantly higher than the proportion of patients with semantic impairment (χ^2 = 5,751; Df = 1; p = 0,016). Moreover, 1/52 patients showed either phonological or semantic deficit exclusively, while an exclusive morphosyntactic deficit was observed in 6/52 patients. Finally, 4/52 patients presented both phonological and semantic impairments, 10/52 both phonological and morphosyntactic impairments, 4/52 both semantic and morphosyntactic impairments, and 17/52 showed impairments in the three domains of language (table 12).

b. Use of the BERA tool in severely brain-injured patients

Results from all evaluations are reported in table 13. Neuroimaging data are also presented in figure 15.

Patient 1

This patient showed reproducible command-following capacity during the CRS-R assessments and was consequently diagnosed as MCS+. The BERA total score (i.e., 21/30; t = -1,836; p = 0,036) was significantly lower than the mean of AC patient. Regarding the BERA sub-scores, morphosyntactic performance (i.e., 5/10; t = -2,634; p = 0,006) was significantly impaired as compared to the AC patients. On the other hand, the phonological (i.e., 8/10; t = -0,512; p = 0,305) and semantic (i.e., 8/10; t = -1,112; p = 0,136) sub-scores were similar to those of the AC patients. A significant difference was detected between the left and right presentation of items (χ^2 = 3,968; Df = 1; p = 0,046), suggesting the presence of spatial neglect, but not between simple and complex items (χ^2 = 0,159; Df = 1; p = 0,919). This finding is the opposite of the behavior of AC patients who showed a complexity effect but no left-right dissociation.

These results indicate the presence of particularly poor performance for the comprehension of morphosyntactic items as compared to the AC patients. Performance on the phonological and semantic items rather reveals the presence of phonological and semantic deficits of similar severity as those characterizing the AC group. The comprehension of sentences compared to words obviously requires a higher cognitive load involving more cognitive functions such as executive functions or verbal short term memory (Key-DeLyria & Altmann, 2016; Tan & Martin, 2018; Zakariás et al., 2018). Morphosyntactic processing could thus have been impacted by executive dysfunctions, which are suggested by the extended bilateral frontal hypometabolism (Badre & Nee, 2017; Munro et al., 2017). Still, this patient presents receptive language difficulties and a partially impaired consciousness, which further correspond to grey matter volume decreases in both

left temporo-occipital fusiform gyrus (Binder et al., 2009) and thalamus (Di Perri et al., 2016; Vanhaudenhuyse et al., 2011).

Patient 2

Patient 2 was diagnosed as EMCS since he was able to functionally use some objects and communicate with a yes/no code. No significant differences were highlighted between the BERA scores of this patient and those of the AC patients (total score: 22/30; t = -1,477; p = 0,073; phonology: t = -1,345; p = 0,092; semantic: t = -1,114; p = 0,135; morphosyntax: t = -1,095; p = 0,139), suggesting deficits of similar severity for all language aspects. Moreover, no left-right (χ^2 = 0,682; Df = 1; p = 0,409) nor simple-complex (χ^2 = 0,682; Df = 1; p = 0,409) dissociations were detected.

This patient presented the best CRS-R diagnosis since he was able to functionally communicate, and he also showed the best BERA total score (i.e., 22/30). In line with these behavioral data, a relative preservation of brain glucose metabolism was also observed in left-sided cortical regions (Binder et al., 2009; Dronkers et al., 2004) This patient however showed grey matter atrophy in the left temporo-parietal junction (Binder et al., 2009), and the comprehension impairments in the three domains of language would be similar to those of the AC patients, including the gradient of difficulty (from semantics to phonology and then morphosyntax).

Patient 3

The third patient had a palpebral ptosis which prevented the evaluation of arousal. Nevertheless, he showed systematic responses to command and intentional communication, leading to the diagnosis of MCS+. Regarding the administration of the BERA, the patient required some help from the examiner in order to keep his eyes opened. In comparison with the AC patients, his BERA total score was significantly lower (i.e., 16/30; t = - 3,630; $p < 0.001$), with particularly poor scores on the semantic (i.e., 6/10; t = -3,178; p < 0,001) and morphosyntactic (i.e., 2/10; t = -4,943 avec p < 0,001) items. However, phonological items (i.e., 8/10; t = -

0,512 avec p = 0,305) did not show any significant difference with those of the AC patients. These results could suggest relatively mild impairment for phonological items, and severe impairment for semantic and morphosyntactic items. No difference was found between left and right presentation of items (χ^2 = 0; Df = 1; p = 1); the difference between complex (i.e., 5/15) versus simple (i.e., 11/15) items was however statistically significant (χ^2 = 4,821; Df = 1; p = 0.028).

The results of patient 3 should be cautiously interpreted given the palpebral ptosis, as well as the diabetes which prevented to obtain reliable FDG-PET data. Regarding the BERA scores, the semantic and morphosyntactic deficits seemed more severe than the phonological impairment. Moreover, an effect of item complexity (as classically observed in aphasic patients) was shown, and particularly concerning the semantic subscale (i.e., 5/5 for simple items versus 1/5 for complex items). One could consequently hypothesize the presence of severe semantic deficits. These results are in line with a decrease of grey matter volume in the left temporal lobule (posterior superior and middle temporal gyri; Saur et al., 2008).

Patient 4

This patient showed visual pursuit and was therefore diagnosed as MCS-. His BERA total score (i.e., 16/30; t = -3,630; p < 0,001) as well as semantic (i.e., 6/10; t = -3,178; p < 0,001) and morphosyntactic (i.e., 3/10; t = -4,174; p < 0,001) sub-scores were significantly lower than those of the AC patients. Nevertheless, the phonological sub-score (i.e., 7/10; t = -1,344; p = 0,092) was in the same range as observed in AC patients. Like patients 1 and 3, this patient showed particularly severe language impairment for the morphosyntactic items. The scores did not differ in terms of level of complexity (χ^2 = 0,536; Df = 1; p = 0,464) and there was no significant difference between left and right item presentation of items (χ^2 = 0; Df = 1; p = 1).

Table 13. Demographical data, scores using the CRS-R and the BERA, brain metabolism results and main hypothesis regarding the DoC patients.

		DoC 1	DoC 2	DoC 3	DoC 4
Best CRS-R	**Total score**	11/23	23/23	15/23	9/23
	Auditory function	3	4	4	1
	Visual function	3	5	3	3
	Motor function	2	6	5	1
	Oromotor/verbal function	1	3	2	2
	Communication	0	2	1	0
	Arousal	2	3	N/A	2
	Diagnosis	MCS+	EMCS	MCS+	MCS-
BERA	**Total score**	21/30*	22/30	16/30*	16/30*
	Phonology	8/10	7/10	8/10	7/10
	Semantic	8/10	8/10	6/10*	6/10*
	Morphosyntax	5/10*	7/10	2/10*	3/10*
Brain areas showing significant hypometabolism		Frontal lobules (median superior and left inferior [pars opercularis] frontal gyrus and right frontal pole), paracingulate and posterior cingulate gyri, bilateral caudate, left thalamus	Left frontal pole and frontal orbital cortex, right inferior temporal, supramarginal gyri	N/A	Left hemisphere, including the left temporal lobule and the Heschl's gyrus
Brain areas showing relatively preserved metabolism		Occipital areas and cerebellum	Left premotor cortex, temporo-parietal and temporo-occipital regions, right occipital fusiform and precentral gyri	N/A	Right parahippocampus and hippocampus, left insular cortex and precentral gyrus
Grey matter atrophy		Left temporo-occipital fusiform gyrus, right frontal orbital cortex, right caudate, left thalamus	Bilateral posterior temporal gyri, left supramarginal gyrus, parietal operculum cortex and frontal lobule, precuneus and thalamus	Right amygdala, left temporal lobule, left insular cortex, right precentral and paracingulate gyri, right insular cortex, planum polare and angular gyrus	Right Heschl's gyrus, temporal pole, supplementary motor cortex, temporo-occipital fusiform cortex and lingual gyrus, and left amygdala, posterior superior temporal gyrus, angular gyrus, thalamus

** scores which are significantly lower than the group of aphasic conscious (AC) patients; DoC: disorders of consciousness; CRS-R: Coma Recovery Scale-Revised; BERA: Brief Evaluation of Receptive Aphasia; MCS: minimally conscious state; EMCS: emergence from the minimally conscious state; N/A: not applicable.*

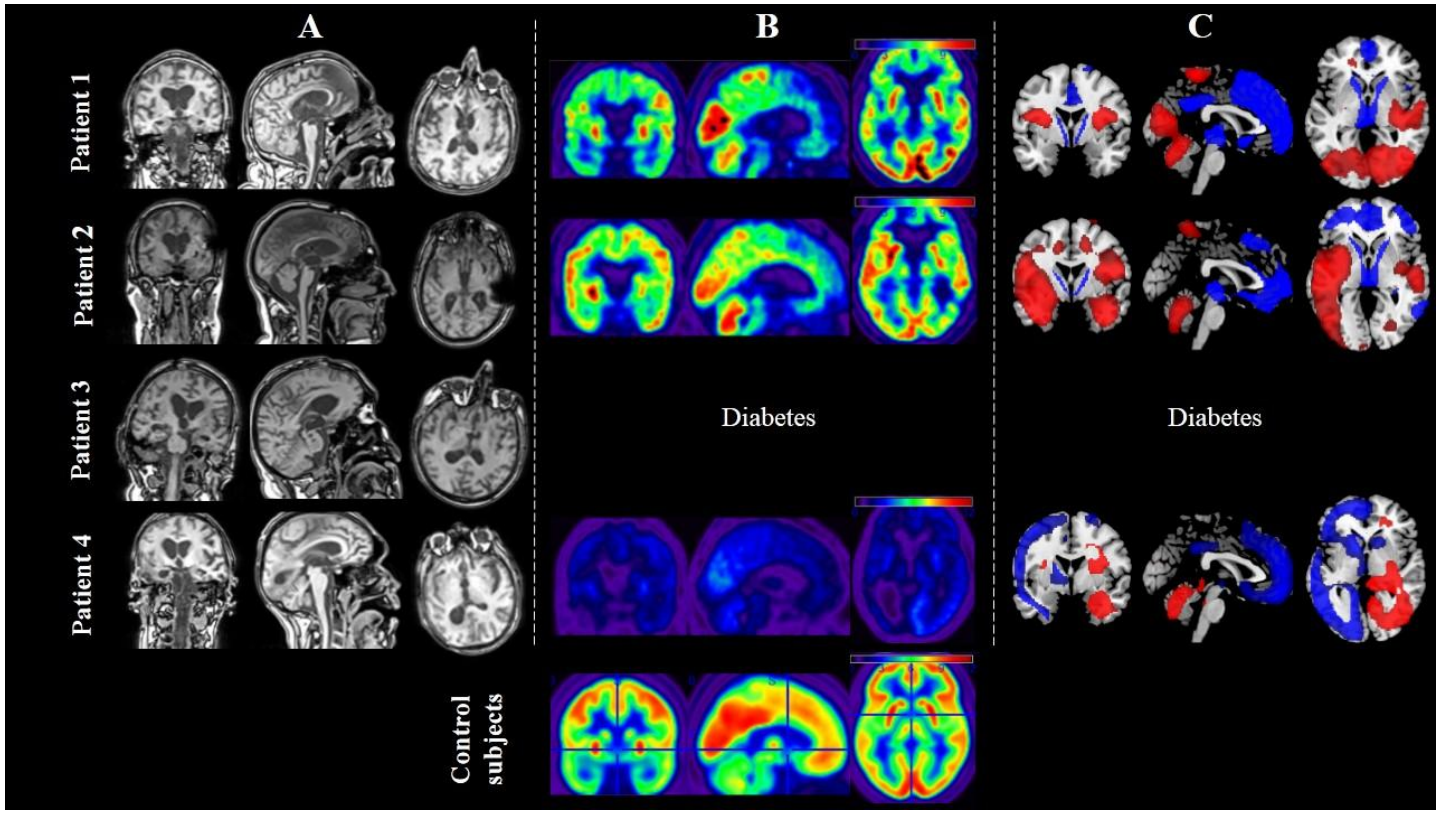

Figure 15. *Brain structure and glucose metabolism in MCS/EMCS patients as assessed with FDG-PET. (A) T1 images of the four patients. (B) Standardized uptake value (SUV) in patient 1, 2 and 4, as well as mean SUV in 34 healthy control subjects. (C) Comparison of global brain metabolism between each patient and the group of healthy control subjects: significant hypometabolism (in blue) and relatively preserved metabolism (in red) at $p < 0,05$ corrected for FDR.*

Patient 4 presented the lowest CRS-R score since he was not able to follow simple commands, and his BERA total score was close to chance (i.e., 16/30). Accordingly, the patient also presented an extended left-sided hypometabolism and grey matter atrophy of the left posterior superior temporal gyrus (Binder et al., 2009; Saur et al., 2008).

4. Discussion

This study aimed to fill a gap in the assessment of language comprehension in DoC patients (Aubinet, Murphy, et al., 2018; Schnakers et al., 2014), through the development of a new assessment tool characterizing receptive language impairment in these patients.

We obtained promising results in terms of psychometric properties, based on the AC patient data. A good internal consistency was shown, particularly for the first three parallel versions. As expected, an effect of item complexity was also reported. Moreover, the BERA also showed good concurrent validity with the LAST language assessment tool. Finally, the BERA showed satisfactory intra- and inter-rater reliability. As regards the DoC patients, the language difficulties that were identified were in line with their CRS-R diagnosis and with a decrease of grey matter volume and/or brain glucose metabolism in several language processing areas. For patient 4, who did not present any language-related sign of consciousness and who performed close to chance at the BERA assessment, it is difficult to determine whether this patient showed the most severe aphasic symptoms or whether he had additional concurrent cognitive deficits preventing any functional communication, independently of language status. Given the extent and severity of the lesions of this patient, it is likely that both language and cognitive deficits were involved.

The comparison of the phonological, semantic and morphosyntactic sub-scores is of particular interest for this study. In AC patients, the semantic subscale led to the highest scores, followed by the phonological subscale, and the morphosyntactic subscale was the most often failed (i.e., at least one error). The most frequent co-occurrence of deficits concerned phonological and morphosyntactic impairments. In contrast, DoC patients rather showed a gradient of difficulty from phonology to semantics, and then to mophosyntax. The phonological subscale was indeed the one presenting the best performance in patients 1, 3 and 4 (who were the most impaired patients), and the phonological sub-scores of all four patients were not significantly lower than the mean of AC patients. On the contrary, semantic and morphosyntactic abilities were significantly impaired as compared to the AC group. This seems therefore atypical for aphasia, and indicates that the particularly poor performance of DoC patients for these subscales stems from difficulties accessing to higher levels of language processing, which are also those acquired later during language development (Friederici, 2005). In these patients with extended brain lesions, additional attention and consciousness impairments might explain why the BERA scores were much lower in the DoC patients as compared to the AC patients.

Besides the distinction between the three language domains, the BERA might also help to detect command-following in post-comatose patients, which is a critical and challenging aspect of DoC assessment (e.g., Edlow et al., 2017; Naci et al., 2018; Owen et al., 2006), as our tool proposes items that are similar to the CRS-R "object-related response to command" (based on eye fixation). The "look at" commands are here repeatedly pronounced, which could indeed help patients with slow cognitive processing to get involved and produce eye responses. As it was demonstrated using the CRS-R (Wannez, Heine, et al., 2017), the BERA assessments could be repeated in DoC patients to obtain more reliable information. Indeed, in these patients both level of responsiveness and visual fixation and pursuit might fluctuate within hours and days (Candelieri et al., 2011; Cortese et al., 2015; Piarulli et al., 2016), and the presence of fatigue or visual difficulties (such as the palpebral ptosis of patient 3) could impact the evaluation of comprehension.

Our study is not without limitation. First, the cognitive profiles of DoC patients' still remain difficult to interpret. Specifically, the BERA scores could reflect the presence of aphasia or rather a language system which has not yet been fully 'reactivated', and for which only the earliest aspects (i.e., phonological processing) are moderately functional. Moreover, this study only included four DoC patients. More post-comatose patients should therefore be assessed using the BERA, the CRS-R and neuroimaging techniques, allowing for group-level analyses. The use of an eye-tracking setting should finally be tested to obtain objective measures of eye fixation in this challenging population.

In conclusion, in this last study we present a new assessment tool for receptive language abilities in post-comatose patients with severe brain injury. The BERA appears as a good tool to complement the CRS-R and other neurological examinations aiming at diagnosing the DoC. The comparison of phonological, semantic and morphosyntactic subscales also brings a strategic cue for language therapists in order to orientate their care and choose the best therapeutic strategies. Nonetheless, the interpretation of all combined data of a DoC patient is necessary in order to better understand his/her cognitive profile. This research presents obvious clinical implications and opens numerous prospects for the future.

General discussion and perspectives

In this thesis, we aimed to improve the identification of residual language abilities in DoC patients. To do so, we first investigated the neural correlates of language-related CRS-R items, which are observed in MCS+ but not in MCS-. Secondly, we used two new behavioral tools to estimate residual language comprehension in DoC patients: the CAVE and the BERA. Our main findings and their clinical implications are here discussed, and various perspectives are exposed.

The assessment of residual language in post-comatose patients with disorders of consciousness (DoC) is limited by their poor behavioral repertoire. Besides, language impairment such as receptive aphasia might prevent consistent responses to verbal instructions, leading to an underestimation of the level of consciousness in post-comatose aphasic patients (Schnakers et al., 2014). This issue has important clinical as well as theoretical implications, as language and consciousness impairments are difficult to disentangle. Accordingly, this thesis mainly aimed to explore residual language abilities in DoC patients after severe brain injury.

1. Synthesis of results

We first investigated behavioral and neuroimaging evidence of residual language abilities in DoC patients through the process of a systematic literature review. Data was extracted for four main outcomes: (1) bedside language behavioral assessments, (2) language-related signs of consciousness, (3) detection of covert command-following and communication using brain-computer interfaces, and (4) cortical activity related to speech processing.

The outcomes 3 and 4 mainly required EEG and/or fMRI techniques to highlight the presence of residual language comprehension abilities in several DoC patients. Active paradigms allowed to detect (covert) command-following capacity, involving sentence comprehension, while passive paradigms recorded differential cortical response to speech versus noise, semantically unambiguous/congruous versus ambiguous/uncongruous sentences, or semantically related versus unrelated words. The temporal lobules (i.e., middle and superior temporal gyri), left angular gyrus and left inferior frontal gyrus were shown to be involved in speech processing in several patients, and the presence of N400 effects in fronto-centro-parietal areas was also related to residual semantic processing in DoC patients.

Only few studies were however reported on the behavioral assessment of residual language function, as based on language-specific tools (i.e., outcome 1) or on the Coma Recovery Scale-Revised (CRS-R) (i.e., outcome 2). As previously recommended by Majerus et al. (2009), we here combined behavioral and neuroimaging assessments to better explore language functions in DoC patients.

Preserved command-following, intelligible verbalization and/or intentional communication in line with more preserved language areas

The outcome 2 was addressed using three retrospective studies in this first part. The neural correlates of the clinical MCS sub-categorization were explored, based on the presence (i.e., MCS+) or absence (i.e., MCS-) of language-related signs of consciousness as assessed by the CRS-R. In general, language areas were more activated in MCS+ compared to MCS-.

Specifically, Study 1 examined brain glucose metabolism in 57 MCS patients by means of FDG-PET. This technique traces changes in glucose metabolism and provides measures of high sensitivity for brain activation, particularly to identify MCS patients (Stender et al., 2014). Our findings suggest that brain function in the language network is determinant for recovery of language-related signs of consciousness. Indeed, the MCS+ group presented higher metabolism mainly in the left middle temporal cortex, left angular gyrus, left inferior and middle frontal gyrus, compared to the MCS- group. The left angular gyrus was also functionally disconnected from the left prefrontal cortex in MCS- compared to MCS+ (i.e., frontoparietal network). Grey matter structure was also assessed in this study by means of voxel-based morphometry (VBM) in 66 MCS patients. Using this technique, every subject's brain is normalized to a template and atrophy is quantified voxel-wise, indicating possible reduction of grey matter volume. No significant differences were found in grey matter volume between patient groups. Note that only potential differences between DoC were previously shown using this technique (Guldenmund et al., 2016).

Study 2 further explored brain function underlying the MCS sub-categorization by means of resting state fMRI. This technique is non-invasive and more suitable than FDG-PET to detect rapid changes in brain activation. Moreover, resting state fMRI networks may contribute to the distinction of DoC (e.g., Demertzi et al., 2015), even if less accurately than brain glucose metabolism (Stender et al., 2014). As MRI examinations often require patient sedation to avoid movement artifacts (therefore preventing acquisition of valid functional data), only 19 MCS patients were included in the present study. Nine of them also had participated in our previous study (for VBM analyses exclusively). Again, higher connectivity was found in MCS+ compared to MCS- in the left frontoparietal network (i.e., executive language control network), here specifically between the left dorso-lateral prefrontal cortex and left temporo-occipital fusiform cortex, involved in semantic processing. In line with our hypotheses, MCS+ and MCS- groups would however not be differentiated by networks associated to auditory processing, perception of surroundings and internal awareness, nor by inter-hemispheric integration and structural brain damage. No significant differences were indeed observed between both subcategories respectively in the auditory network, right frontoparietal network, default mode network, thalamocortical and interhemispheric connectivity, between-network anticorrelations and grey/white matter volume.

The observed between-group difference in the left frontoparietal network was thus particularly consistent across studies (Aubinet et al., 2020; Aubinet, Larroque, et al., 2018; Bruno et al., 2012), either according to FDG-PET or fMRI measurements. Hence, MCS patients and healthy control subjects could be placed along a continuum, from severe left frontoparietal network dysfunction, possibly associated to severely impaired language processing in MCS- patients, to preserved network connectivity in healthy subjects, with MCS+ patients being situated between these two groups.

The neural correlates of the MCS sub-categorization were reported through cross-sectional studies so far. Given the clinical relevance of such patient sub-categorization, we also aimed to provide longitudinal data of patients who were

firstly diagnosed as MCS- and then as MCS+ after having recovered language-related signs of consciousness (i.e., command-following). The number of patients who were twice hospitalized and assessed by our team is limited, and only three patients met the inclusion criteria for our Study 3; one of them was also included in our Study 1 (for both FDG-PET and VBM analyses). At the second time point, all three patients showed less hypometabolism and/or higher grey matter volume in regions previously associated to self-consciousness such as the precuneus and thalamus, as well as in language-related regions such as the left caudate and temporal/angular cortices. This latter result is in line with Study 1 and Study 2. Here, both FDG-PET and VBM techniques however allowed differentiating the MCS- and the MCS+.

Differences between MCS subcategories in grey matter structure were thus only revealed at the individual level. One could argue that the effect was less powerful than inter-subject variability in our group analyses, which could explain its appearance only within the same subject. Analyses such as VBM present some limitations, such as the aggregation of data on the group level (Guldenmund et al., 2016). On the other hand, our third study only presented two cases showing grey matter volume recovery in line with command-following reappearance. Further studies should use other techniques measuring brain structure alterations to determine if MCS+ patients have actually more preserved grey matter compared to MCS- patients. For instance, regional brain volumetry at the single-subject level recently allowed to distinguish MCS patients from those with an unresponsive wakefulness syndrome (Annen, Frasso, et al., 2018).

The CAVE and BERA tools to complement the CRS-R and neuroimaging assessments

Our work then focused on bedside language assessment attempts in DoC patients, addressing the outcome 1 in two prospective studies. New behavioral tools were here developed and used in comparison with CRS-R, FDG-PET and VBM.

Study 4 presents the Cognitive Assessment by Visual Election (CAVE), which was elaborated and validated by Murphy (2018) to assess recognition of objects, pictures, letters, numbers, written words and colors in patients in MCS or emerging from the MCS (EMCS). For time constraints reasons, we could only recruit 5 patients: maximum one patient was hospitalized per week and preserved visual fixation and pursuit capacities were required. For each included patient, the CAVE scores decreased in line with the CRS-R total score, establishing a consistent behavioral/cognitive profile. All patients showed structural and functional brain impairments corresponding to their behavioral/cognitive profile as based on previous literature. For instance, the patient with highest CRS-R and CAVE scores also showed the least extended hypometabolism. Brain-behavior relationships might thus be hypothesized even in severely brain-injured patients.

As the CAVE does not distinguish various language domains nor include any control of psycholinguistic effects (e.g., word length or frequency), we finally elaborated the Brief Evaluation of Receptive Aphasia (BERA). This tool assesses receptive phonology, semantics and morphosyntax based on visual selection of a target-picture next to a specific distractor. Study 5 describes how we administered the BERA tool to 10 healthy subjects (expecting a ceiling effect), 52 aphasic conscious patients and four MCS or EMCS patients. This evaluation showed promising results in aphasic conscious patients, with good intra- and inter-rater reliability and satisfactory internal validity (i.e., similarity between the different versions) and concurrent validity compared to the Language Screening Test (LAST). Unfortunately, our hospitalizations of DoC patients were suddenly interrupted during several months, and we had beforehand only included a few of them. Their BERA scores suggested the presence of specific receptive difficulties for phonological, semantic and particularly morphosyntax subscales. The results were in line with FDG-PET and VBM data. The BERA tool may complement the CRS-R and neuroimaging assessments to diagnose patients' DoC and refine their cognitive and language profile.

Overall, our results provided new insights with regard to the characterization of DoC patients' language residual abilities. These various studies have several clinical implications and constitute a new step toward the disentanglement of consciousness and language impairments in these severely brain-injured patients. Both aspects will be developed in the two next sections.

2. Clinical implications

The neural correlates of language-related behaviors to reduce the MCS misdiagnosis

The investigation of neural correlates of language-related signs of consciousness is clinically relevant as it contributes to reduce MCS misdiagnosis rates. As stated in our introduction, an accurate diagnosis of DoC is indeed crucial for daily management (i.e., pain treatment or stimulation protocols), end-of-life decisions and prognosis (Chatelle et al., 2016; Demertzi et al., 2011; Thibaut et al., 2017).

In line with previous multi-modal studies (Golkowski et al., 2017; Stender et al., 2014), brain glucose metabolism seems to be an accurate marker for the differential diagnosis of DoC, here in particular MCS- and MCS+. Acquisition of resting state fMRI is more challenging since the absence of movement, sleep and sedation in the scanner is essential to obtain valid data. Overall, preservation of glucose metabolism or fMRI connectivity in the left frontoparietal network may suggest the presence of a cognitive-motor dissociation (Edlow et al., 2017; Schiff, 2015) in patients who do not follow command at bedside. The efforts to seek voluntary responses should consequently be intensified in these patients by repeating the behavioral assessments or using brain-computer interfaces (e.g., Annen, Blandiaux, et al., 2018). Similarly, speech therapists should endeavor to obtain any sign of residual language in those patients, by using various material to assess

language, including fMRI or EEG passive paradigms (e.g., Coleman et al., 2007; Owen & Coleman, 2008) whenever possible.

Non-invasive brain stimulation further represents a promising therapeutic approach for both DoC patients (Thibaut et al., 2019; Thibaut et al., 2017) and aphasic conscious patients (Biou et al., 2019; Bucur & Papagno, 2019; Fridriksson et al., 2018). FDG-PET and fMRI data could guide clinicians to target specific brain regions for techniques such as repeated transcranial direct current stimulation. For instance, this stimulation could be applied on top of the cortical representation of the left angular gyrus or temporal lobule in MCS- patients. Indeed, applying such stimulation over a functionally impaired area could potentially induce an increase in brain glucose metabolism (e.g., Yun, Song, & Chung, 2016) and lead to an improvement of language-related behaviors. Still, this hypothesis should be tested prospectively, including neuroimaging evaluations of patients' individual structural and metabolic impairment.

As stated above, our findings also reveal the potential value of VBM analyses at the individual level, as grey matter volume of language areas (e.g., left fusiform, angular and temporal cortices) was shown to be more impaired in two patients when in MCS- compared to MCS+. Another interesting and clinically relevant result was the bilateral structural and functional changes from MCS- to MCS+, suggesting contralateral compensation even in chronic MCS, similarly to what was shown in aphasic conscious patients (Artzi et al., 2016; Teki et al., 2013). Note that the clinical importance of such case studies in neuropsychological research was recently highlighted by Cubelli & Della Sala (2017).

Overall, the first experimental part could be of great help to identify patients with cognitive abilities missed at the bedside, which should improve their rehabilitation care by choosing the most suitable therapeutic strategies. Nevertheless, the use of neuroimaging requires technical settings and expertise, and consequently could be difficult to implement in current rehabilitation centers.

A better detection of language impairment in post-comatose patients

The clinical relevance of the second experimental part is even more obvious since the aim was to fill a gap in the evaluation of language functions in DoC patients, by elaborating and using new behavioral bedside assessment tools, which were combined to neuroimaging techniques.

Classical aphasia tests are not appropriate to detect language deficits in DoC patients as they are long and require preservation of arousal, visual, motor and oro-motor abilities. As previously mentioned, the BERA tool was used in aphasic conscious patients in comparison with the LAST (Flamand-Roze et al., 2011). Most of the LAST items are dedicated to language production and the comprehension items require at least partial preservation of visual and motor functions (e.g., capacity to point at pictures or to follow instructions such as "don't take the drinking-glass but the pen"). If this test is indicated to detect language impairment in acute stroke patients, the presence of massive brain lesions makes it much less feasible in DoC patients.

To our knowledge, the CAVE was the first short scale to focus on the visual modality exclusively, by using a target-image next to a distractor. It was developed by the neuropsychologist Murphy (2018) as a result of her clinical work. Moreover, this choice of visual modality is sustained by our recent findings according to which visual fixation and pursuit are the most often observed signs of consciousness in a population of MCS patients (Wannez, Gosseries, et al., 2017). In our opinion, the CAVE allows a good screening of residual cognition in acute post-comatose and chronic DoC patients, which might possibly lead afterward to more specific neuropsychological tasks. This assessment is also indicated to investigate basic reading abilities. Still, the CAVE does not distinguish various language domains nor include items controlling for psycholinguistic effects such as word length or frequency.

We developed the BERA tool to provide more information to speech therapists in order to refine patients' language profile. This short assessment allows the

distinction of phonological, semantic and morphosyntactic receptive abilities and most items include control of length and frequency. This latter aspect could however be improved in a revised BERA version. The presence of visual deficits crucially prevents the administration of our tool. Language impairment could however be estimated even in a patient with palpebral ptosis by manually opening his eyes. The first eye fixation lasting more than two seconds was taken into account. Yet, some patients may look hesitant in their responses. Scores were consequently based on a consensus between two raters to be as accurate as possible. All good fixations were then scored 1, but we did not specify the reasons of 0 scores. A revised version should better distinguish the "undecided fixation", "bad fixation", or "no fixation" responses. The use of "stop criteria" should also be implemented for patients who cannot carry out the task. Given the poor morphosyntax scores obtained by 3/4 DoC patients, this subscale should finally be optional. It would then be administered as soon as word comprehension in phonological and semantic subscales is not severely impaired. We could consequently keep two out of the four initial BERA versions by retaining the most appropriate items, including diverse possible fixation responses and "stop criteria", as well as proposing an optional morphosyntactic subscale.

Overall, we here demonstrated the feasibility and robustness of the CAVE and BERA assessments in several MCS and EMCS patients, with sub-scores corresponding to their neuroimaging results. These scales could be used to complement the CRS-R in both acute and chronic clinical settings, either to longitudinally follow the recovery of language functions or to establish new therapeutic objectives and strategies. For instance, once patients have recovered the ability to selectively fixate an item, one could imagine a rehabilitation program using pairs of images with distractors of increasing difficulty. Patients would then be stimulated by repetitively asking them to look at the target, which could be phonologically, semantically or mopho-syntactically related, depending on patients' deficits as detected using the BERA.

3. Disentangling DoC and language impairment

By examining language deficits and/or residual abilities in severely brain-injured DoC patients, our studies constitute a new step toward the disentanglement of consciousness and language impairments. In particular, one may ask if MCS- and MCS+ subcategories represent different states of consciousness *per se* or rather distinct cognitive profiles. The first hypothesis would be sustained by our Study 3, where the three patients showed metabolism or grey matter restoration when they were MCS+ in the thalamus and/or precuneus, which are critical for self-consciousness (Di Perri et al., 2016; Vanhaudenhuyse et al., 2011).

According to the second hypothesis, MCS- patients fail to understand commands, establish a communication code or intelligibly verbalize due to a severe impairment of language function. Analogously, MCS+ patients should not be necessarily considered as "more conscious" than MCS- patients. In line with this hypothesis, Study 1 failed to reveal FDG-PET differences in regional brain function regarding specific areas considered to be associated with various aspects of consciousness (e.g., DMN including thalamus and precuneus) (Demertzi, Soddu, et al., 2013; Thibaut et al., 2012), whereas the language network distinguished both MCS subcategories. In addition, the resting state fMRI Study 2 did not show any significant difference between MCS- and MCS+ regarding the DMN and thalamocortical network, whose functional connectivity however increases along with the level of consciousness (Di Perri et al., 2016; Zheng et al., 2017). Functional connectivity of the auditory network did also not differ between MCS groups whereas this network was found with the highest discriminative capacity for distinguishing UWS and MCS patients (Demertzi et al., 2015).

It is however important to note that, even if activity of the DMN was associated to the level of consciousness in numerous studies (e.g., Demertzi et al., 2015; Di Perri et al., 2016; Vanhaudenhuyse et al., 2011), these regions may also be involved

in other processes such as cognitive functions (Leech et al., 2011) or discrete emotions (Satpute & Lindquist, 2019). The absence of significant difference between MCS- and MCS+ subcategories might therefore reflect comparable capacities regarding these processes rather than a similar level of consciousness.

Still, these hypotheses raise theoretical questions about the categorization of DoC, which could be considered as a sum of focal dysfunctions (Pistoia et al., 2013), including language impairment, rather than a global brain dysfunction. In line with this, an interesting study proposed to revise the taxonomy of DoC to better capture patients' performance across various cognitive and behavioral tasks including neuroimaging measures (Bayne, Hohwy, & Owen, 2017). According to the authors, the assignation of covertly conscious nonresponsive patients to the 'cognitive-motor dissociation' category would not be sufficient to account for patients' residual abilities and their progressive recovery. They suggested that current discrete DoC categories could be replaced by graded entities from a multidimensional framework. An example of structure could include 8 dimensions: global incongruency detection, metacognition, executive control, visual tracking and fixation, volition control, attentional control, speech production and semantic comprehension (as based on Bayne, Hohwy, & Owen, 2016 and Sergent et al., 2017). Such new DoC taxonomy would thus attach more importance to patients' language functions; it would however require the modeling of relationships between the various behavioral, cognitive and neural capacities of patients.

4. Quality assessment

The present studies had several limitations that were already exposed in their respective section. We here propose to assess their quality using the same criteria as in our systematic review (i.e., QUADAS-2 criteria, see Introduction) (Whiting et al., 2011).

First, patient selection could have introduced biases as all studies recruited a convenience sample of DoC patients, which are rare cases. In the retrospective studies of our first experimental part, we included all patients meeting our inclusion criteria to ensure the best possible statistical power. As mentioned above, we could only include a few DoC patients in both prospective studies of our second experimental part, leading to two case series. In this respect, all our studies presented high risk of bias with regard to the population.

Second, the conduct of the index test in the first experimental part (i.e., neuroimaging assessments) could have led to biases as all FDG-PET, VBM and fMRI analyses were performed with knowledge of the results of the CRS-R (patients' MCS- or MCS+ diagnosis). The studies of the second experimental part also showed high risk of bias regarding the CAVE and BERA assessments, which were done without blinding of CRS-R scores.

Third, we always employed repeated CRS-R as our reference standard, therefore using well-established criteria (Giacino et al., 2004; Wannez, Heine, et al., 2017). Moreover, the CRS-R scores were interpreted without knowledge of the results of the index test. Consequently, we conclude that the CRS-R conduct and interpretation could not have generated other biases.

Fourth, an appropriate interval between index test and reference standard was respected in all our studies, as one CRS-R was performed on the day of neuroimaging and language behavioral assessments. All recruited patients received the same reference standard and all of them were also included in the analyses. Hence, the patient flow and timing presented low risk of bias.

Overall, the main risks of bias come from patient selection as well as lack of blinding of CRS-R scores with regard to the interpretation of the index test. Note that the population (DoC patients), index test (neuroimaging and language assessments) and reference standard (CRS-R) well correspond to the initial review question.

5. Perspectives

Future studies are needed to address these concerns and develop new strategies aiming at better characterizing language and consciousness impairments in this population of DoC patients.

The sub-categorization of the MCS based on CRS-R language-related items should further be investigated using other recent techniques. As an example, the white matter neural correlates of MCS- versus MCS+ could be explored by means of diffusion tensor imaging (DTI), as based on the language dual-stream pathway (see figure 16) identifying two auditory comprehension networks: a left-sided dorsal network associated with auditory-motor integration and phonology, and a more bilateral ventral network involved in voice processing, semantics and syntax. The first one contains the superior longitudinal and arcuate fascicles from the posterior superior temporal gyrus via the parietal lobe to the inferior frontal cortex (Saur et al., 2010; Specht, 2014), whereas the ventral network includes fibers of the capsula extrema between middle temporal gyri, fusiform gyrus and ventrolateral prefrontal cortex (Saur et al., 2010). These fibers may be reconstructed using diffusion analysis techniques in order to quantify the level of white matter integrity in both MCS- and MCS+ patients, expecting more impaired structure in the first group.

In another future perspective, information about brain glucose metabolism and functional connectivity differences between MCS- and MCS+ categories might be integrated into machine learning classifiers, in line with previous research allowing the differentiation between UWS and MCS (Demertzi et al., 2015). When used at the single subject-level, machine learning classifiers could consequently enhance the diagnostic accuracy and sensitivity of MCS patients.

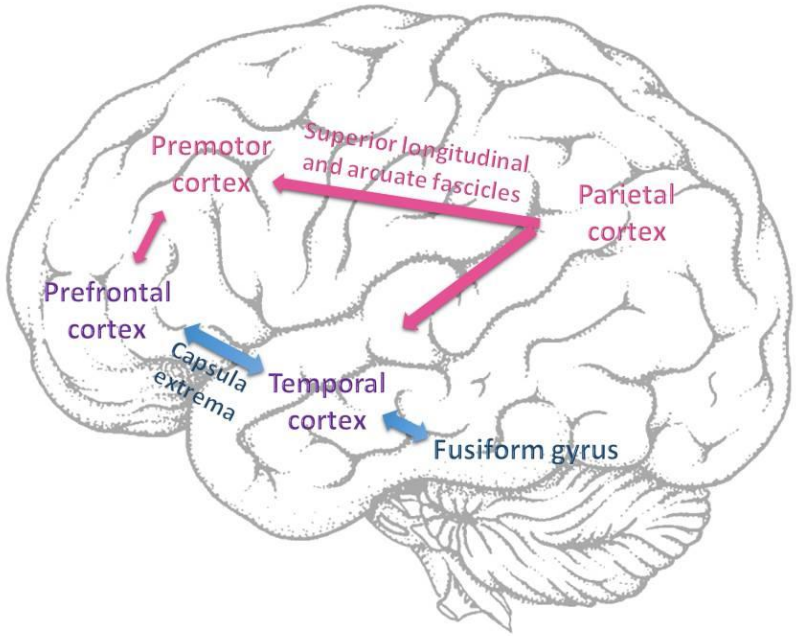

Figure 16. *Functionally and anatomically defined brain networks subserving phonological (dorsal network in pink) and semantic processing (ventral network in blue).*

On the other hand, the administration of the CAVE and BERA tools to DoC patients presents several prospects for the future. Both new scales may help to better characterize patients' cognitive profile (and actual level of consciousness) by complementing the CRS-R. Indeed, according to Bayne, Hohwy and Owen (2017), behavioral capacities as assessed by the CRS-R are only one manifestation of consciousness, and there is now overwhelming evidence that consciousness can occur in DoC patients in the absence of any intentional behavior (e.g., Harrison & Connolly, 2013).

First, some studies should aim to optimize the CAVE and BERA bedside assessments. Crucially, more DoC patients should be assessed in the future using the BERA, allowing validation and analyses of psychometric properties in acute and chronic post-comatose patients. Unlike the CAVE, the BERA was elaborated in French and validated in French-speaking patients. To ensure larger diffusion possibilities, a next major step would be to translate and validate this scale in English and other languages. Since many DoC patients have visual difficulties (e.g.,

palpebral ptosis, nystagmus), the additional use of an eye-tracking system could better detect eye fixations, as compared to one or even two examiners. Hence, future studies should adapt such device to the administration of the CAVE and the BERA in order to obtain more objective measures. Given patients' circadian variations in diverse residual abilities (Candelieri et al., 2011; De Weer et al., 2011), assessments using these scales could also be repeated to obtain more reliable information, as it was demonstrated using the CRS-R (Wannez, Heine, et al., 2017).

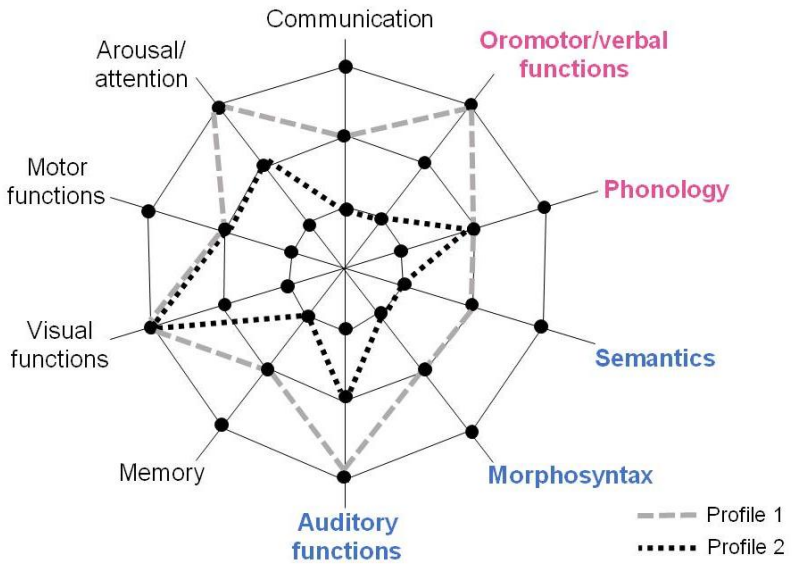

Figure 17. *Two expected severely brain-injured patients' profiles based on Study 5. (1) Severe aphasic profile with motor impairment, possible recovery of command-following and BERA performance similar to aphasic conscious patients; (2) Severe cognitive and motor profile with language also impacted by concomitant attention and memory deficits.*

Importantly, the analysis of DoC patients' profile with interactions between their residual behavioral capacities may contribute to use a new multidimensional framework as suggested by Bayne, Hohwy and Owen (2017). Figure 17 illustrates a 10-dimension framework and the extraction of typical patient profiles according to the CRS-R (auditory, visual, motor and oro-motor functions as well as communication and arousal/attention), the CAVE (visual memory task) and the BERA (phonology, semantics and morphosyntax). These new tools could therefore

help establishing a new taxonomy of DoC accounting for patients' residual behavioral abilities including language.

Second, the neural correlates of residual language as assessed by the BERA could be investigated using diverse techniques. In particular, one could hypothesize that DoC patients presenting dissociations between the scores at the phonological and semantic sub-scales would also show the corresponding functional impairment of dorsal or ventral comprehension networks (figure 16) using FDG-PET and resting state fMRI. In the same idea, BERA assessments could be compared to DTI data, expecting an alteration of arcuate and superior longitudinal fascicles in case of severe phonological impairment, and an alteration of capsula extrema fibers in case of severe semantic impairment.

Furthermore, both passive and active paradigms could be elaborated based on the BERA items using either fMRI or EEG. A passive paradigm would measure patients' cortical activity in response to the auditory items of the BERA (i.e., pairs of related versus unrelated words and sentences). In line with previous studies, the contrast between semantically related and unrelated words would induce an EEG N400 effect (Beukema et al., 2016; Rohaut et al., 2015) and fMRI activations in the middle temporal gyrus and angular gyrus (Nigri et al., 2017). An active paradigm would involve the visual presentation of BERA pictures together with the auditory items, either in the scanner or with electrodes over the scalp. Such research would go beyond the fMRI studies of Monti et al. (2013) and Rodriguez-Moreno et al. (2010), which respectively estimated patients' capacity to recognize faces versus houses or to silently name pictures, as well as beyond the EEG study of Pan et al. (2014), which detected in two DoC patients the ability to selectively fixate on command their own photo or an unfamiliar photo. Importantly, such new paradigms could inform about DoC patients' residual comprehension abilities (as compared to aphasic conscious patients or healthy subjects), even in the absence of actual fixation of targets during the bedside BERA assessment.

To conclude, some interesting trends were drawn with regard to the neural correlates of language-related signs of consciousness (i.e., command-following, intelligible verbalization and intentional communication) as assessed by the CRS-R. The investigation of these neural correlates might contribute to identify patients with cognitive abilities missed at the bedside. Other recent techniques would provide new information about MCS subcategories, and machine learning classifiers should also be developed to complement behavioral assessments in the diagnosis of DoC. The CAVE and BERA assessments were further presented as robust tools to complement neuroimaging and classical behavioral scales dedicated to post-comatose patients. Yet, their administration should be repeated and optimized in future behavioral studies on larger samples of DoC patients. Neural correlates of receptive phonological, semantic and morphosyntactic residual abilities in this population should finally be investigated by combining BERA assessments and neuroimaging or EEG, either consecutively or simultaneously.

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Appendices

Supplementary material of studies

Appendix I. *Language residual abilities in patients with disorders of consciousness as assessed with behavioral bedside assessment, electrophysiology and neuroimaging: A systematic review.*

Appendix II. *Brain metabolism but not grey matter volume underlies the presence of language function in the minimally conscious state.*

Appendix III. *The clinical sub-categorization of minimally conscious state according to resting functional connectivity.*

Appendix IV. *Reappearance of command-following is associated to recovery of language and consciousness networks: A longitudinal multiple-case report.*

Appendix V. *Brain, behavior and cognitive interplay in disorders of consciousness: A multiple case study.*

Appendix VI. *Validation of the Brief Evaluation of Receptive Aphasia for detection of specific language impairment in severely brain-injured patients.*

Language residual abilities in patients with disorders of consciousness as assessed with behavioral bedside assessment, electrophysiology and neuroimaging: A systematic review.

Supplementary material

Supplementary material 1. Diagnostic criteria of disorders of consciousness.

Supplementary material 2. Methods of the systematic review.

Supplementary material 3. Results of the systematic review.

Supplementary material 4. Quality assessment of the studies included in the systematic review.

Supplementary material 1. Diagnostic criteria of disorders of consciousness

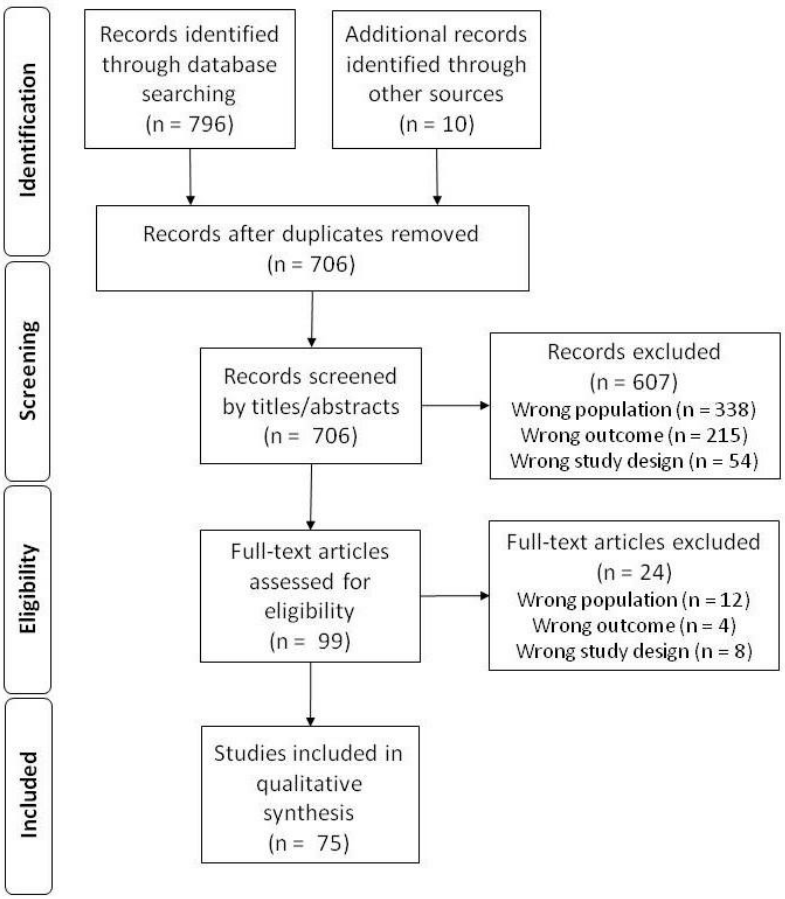
Disorder of consciousness	Diagnostic criteria	References
Coma	Eyes always closed Duration: > 1h Recovery from coma: few hours to 4 weeks	Laureys & al. (2004). Brain function in coma, vegetative state, and related disorders, *Lancet Neurology*, *3*(9), 537-546.
Unresponsive wakefulness syndrome (i.e. vegetative state)	Eye opening Partially preserved sleep-wake cycles Absence of purposeful behaviors Absence of language Preserved hypothalamic and brainstem autonomic functions	The Multi-Society Task Force on Persistent Vegetative State guidelines (1994). *The New England Journal of Medicine*, *330*(22), 1572-1579. Laureys & al. (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome, *BMC Medicine*,8(68).
MCS-	Oriented (contextualized) behaviors Visual pursuit or fixation Orientation to noxious stimulation Reaching for objects Contingent behaviors (emotional)	Giacino & al. (2002). The minimally conscious state: definition and diagnostic criteria, *Neurology*, *58*(3), 349-353. Bruno & al. (2011). From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: Recent advances in our understanding of disorders of consciousness. J Neurol 258:1373–1384.
MCS+	Following simple commands Intentional communication Intelligible verbalization	
Emergence from MCS	Functional communication AND/OR Functional object use	Giacino & al. (2002). The minimally conscious state: definition and diagnostic criteria, *Neurology*, *58*(3), 349-353.

Supplementary material 2: Methods of the systematic review

The method was defined in advance and documented in a protocol, in compliance with established recommendations for conducting systematic reviews, i.e. the PRISMA guidelines.(Moher et al., 2015) The full review protocol is presented in supplementary material 1. It was registered in PROSPERO prior to the beginning of the study.

Inclusion criteria

Studies were included in the systematic review if they met the following criteria: (1) population composed of adult patients (> 16 years old) with DoC following severe acquired brain injury; (2) intervention including any language bedside assessments, neuroimaging or electrophysiology with linguistic stimulations or focusing on language networks/areas; (3) enabling to detect residual language abilities (speech comprehension and/or production); (4) English-speaking studies from peer-reviewed journals; and (5) publication from after the 2002 consensus-based criteria for diagnosing MCS.(J T Giacino et al., 2002) Literature and systematic reviews were excluded. The selection process is presented in the following flowchart:



Search method

This systematic review selected all relevant studies published between January 2002 and September 2019 in the following electronic bibliographic databases: PubMed (Medline), Ovid (Medline) and Scopus. Primary search terms used defining DoC after brain injury included *consciousness disorders, vegetative state, unresponsive wakefulness, minimally conscious* and *severe brain injury*. These primary terms were paired with secondary terms such as *language (disorders), comprehension* or *speech*. A full description of the Ovid (Medline) search strategy is presented in supplementary material 2. We last searched the electronic databases on September 26, 2019. Additional relevant articles being cited were also identified.

Study selection and data extraction

The RAYYAN QCRI web application (https://rayyan.qcri.org/) was used to merge all search results and remove duplicates. Two investigators (CA and CC) independently reviewed (i.e., blind) titles and abstracts to remove all the publications that were not relevant with our research. A second selection was also performed on the basis of studies' full-texts. Any discrepancies were resolved by consensus, and it was planned that a third investigator (MC) would decide if no agreement could be reached.

The extracted data included: study aims and main topic, number of patients, diagnostic scale, patients' diagnosis and etiologies, intervention, control condition, study design and summary of main results. Data extraction was performed by the same two blinded investigators, any disagreements were discussed, and the third investigator joined the debate if necessary.

Quality assessment

The risk of bias of all individual selected studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2; https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/). This checklist estimates the risk of bias and applicability concerns over four domains: patient selection, index test, reference standard, and flow and timing.(Whiting et al., 2011) Again, both main investigators (CA and CC) independently conducted this assessment, which was then submitted for consensus.

Data synthesis

Selected studies were organized in a table including a comparative synthesis of the findings. Data were synthesized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist. We performed a qualitative narrative synthesis by gathering articles focusing on the same main topic: (i) Bedside behavioral tools developed to assess language processing in patients with disorders of consciousness, (ii) Neural substrates associated with language-related signs of consciousness, (iii) Assessment of covert command-following as a sign of language ability using brain-computer interfaces (mainly electrophysiology and neuroimaging techniques), (iv) Cortical activity in response to speech/auditory stimulations (i.e., using electrophysiology and/or neuroimaging techniques).

Supplementary material 3: Results of the systematic review											
REFE-RENCE	**STUDY DESIGN**	**N PATIENTS**	**N HEALTHY SUBJECTS**	**DIAGNO-SIS**	**ETIO-LOGY**	**AGE (years)**	**GEN-DER**	**TIME POST-ONSET**	**SCALES**	**TECHNI-QUES**	**TASKS & RESULTS**
BEDSIDE LANGUAGE BEHAVIORAL ASSESSMENTS											
Aubinet et al. (2018)(Aubinet, Murphy, et al., 2018)	Prospective multiple case study	5	PET : 34 ; MRI : 36	2MCS-, 1MCS+, 2EMCS	2TBI, 2stroke, 1anoxia	R=20-66	1F	*M*=21.6 *SD*=10.7 R=13-36 months	CRS-R	Behavio-ral PET Structural MRI	The Cognitive Assessment by Visual Election (CAVE) was developed to assess visual recognition of objects, pictures, numbers, letters, written words and colors. Residual language comprehension skills were found using the CAVE (and the CRS-R) in the MCS+ and both EMCS patients, also in the presence of preserved temporal and angular cortex metabolism.
Borer-Alafi et al. (2004)(Borer-Alafi et al., 2002)	Prospective cohort study	42	/	UWS	42TBI	*M*=30.6 *SD*=13.9 R=17-72	15F	*M*=43.6 *SD*=31.2 R=12-212 days	GCS	Behavio-ral	The Loewenstein Communication Scale (LCS) assesses articulation/voice, matching, command-following, object recognition, verbal communication, basic speech, prosody, message quality (intelligibility) and alternative communication. It was proved to be reliable and predictive of rehabilitation progress of MCS patients: a significant difference in auditory comprehension (but not in communication) was found between the group of patients who were referred for continued rehabilitation and the group of patients who did not.
Cheng et al. (2013)(Cheng et al., 2013)	Prospective cross-sectional study	86	/	47UWS, 39MCS	53TBI, 33NTBI	*M*=46 *SD*=17	19F	*Mdn*=5 R=3-13 months	CRS-R	Behavio-ral	When assessing auditory function in DoC (e.g., during CRS-R administration), using the SON is shown to be more suitable to elicit a response as compared to neutral sound. Indeed, 37/86 (43%) patients showed localization to auditory stimulation and more patients (40%) oriented the head or eyes to their own name as compared to ring bell (23%).

Day et al. (2018)(Day et al., 2018)	Retrospec-tive longitudinal study	27	/	?	21TBI, 3anoxia, 2stroke, 1other	*M*=36.5 *SD*=14.7 R=18-69	11F	*M*=88.1 *SD*=134.5 R=13-610 days	CRS-R	Behavio-ral	The CRS-R command-following item was compared with individualized quantitative behavioral assessments (IQBA) involving administration of 4 to 8 command trials. For 22/27 patients, IQBA more consistently documented command-following than the CRS-R, whereas no patients showed the reverse pattern. For 14/20 analyzable patients, IQBA provided earlier evidence of consciousness, for 2/20 patients CRS-R provided earlier evidence, and for 4/20 patients both methods provided initial evidence on the same day. IQBA approaches can provide more consistent and earlier evidence of command-following than the comparable item on the CRS-R.
Rasmus et al. (2019)(Rasmus et al., 2019)	Prospective cohort study	18	/	MCS	?	*M*=25 *SD*=5	?	1months to 7months	GCS, Indivi-dual Commu-nication Skills Scale (ICSS)	Behavio-ral	The Individual Nonverbal Communication Rating Scale proposes measurement of primal, sensory, organized behavior (preverbal), sound, verbal and intrapsychic communications. Preverbal communication, both in primal and sensory areas, increases between Stage II (GCS=6–8 points) and Stage III (GCS=9–12 points). After a time, primal communication reached a high level. Patients produced communication attempts from the behavior organization level, and an increase in the nonverbal communication level was noted.
Yamaki et al. (2018)(Yamaki et al., 2018)	Retrospec-tive cohort study	45	/	1coma, 8UWS, 20MCS, 16 severe neurolo-gical disability	TBI	*M*=36.5 *SD*=15.6 R=17-71	11F	782days	CRS-R, GCS	PET, behavioral	The “Chiba score” consists of 11 items including evidence of language comprehension or expression. FDG uptake was originally high in patients with a high level of wakefulness and small ventricular size. Improvement of total Chiba score, and especially language expression, was shown in the increased FDG uptake group compared to the group with stable FDG uptake value. Spearman’s rank correlation coefficients of change in standard uptake value max and language expression between the first and second PET were 0.4 (p = 0.004).

NEURAL CORRELATES OF THE MCS LANGAGE-RELATED SUB-CATEGORIZATION											
Aubinet et al. (2019)	Retrospec-tive cross-sectional study	87	PET 34 MRI 36	PET 16MCS-, 41MCS+ MRI 17MCS-, 49MCS+	47TBI, 40NTBI	PET MCS-: *M*=42 *SD*=18; MCS+: *M*=39 *SD*=16; MRI MCS-: *M*=38 *SD*=14; MCS+: *M*=43 *SD*=17	PET 23F MRI 27F	PET MCS-: *M*=543 *SD*=571; MCS+: *M*=825 *SD*=901; MRI MCS-: *M*=541 *SD*=509; MCS+: *M*=860 *SD*=1025 days	CRS-R	PET, structural MRI (VBM)	The main findings show metabolic differences in the left-sided language network sustaining the clinical sub-categorization of the MCS, while no grey matter volume differences were found. They suggest that brain metabolism, more than structural damage, is determinant for the recovery of language-related abilities in the MCS. In comparison with the group of MCS- patients, MCS+ patients presented higher metabolism preservation in different language-related areas (i.e., left middle temporal cortex, left angular gyrus, left middle frontal gyrus, left inferior frontal gyrus, prefrontal and premotor cortex as well as supplementary motor area). The functional connectivity analysis showed a disconnection between the left angular gyrus and the left prefrontal cortex/supplementary motor area in MCS- as compared to MCS+ (FWE correction), which could reflect a deficit in language integration in MCS- patients.
Aubinet et al. (2019)(Aubinet et al., 2019)	Retrospec-tive longitudinal multiple case study	3	PET : 34 ; MRI : 36	3MCS- then 3MCS+	2TBI, 1hemor-rhage	R=23-37	1F	R=10-60 months	CRS-R	PET, structural MRI (VBM)	Three patients were MCS- during their first stay and had recovered command-following when they were reassessed (i.e., MCS+). When the three patients were in MCS+, they showed less hypometabolism and/or higher grey matter volume in brain regions such as the precuneus and thalamus, as well as the left caudate and temporal/angular cortices known to be involved in various aspects of semantics. These regions are associated with self-consciousness and language processing.

Aubinet et al. (2018)(Aubinet, Larroque, et al., 2018)	Retrospective cross-sectional study	19	35	9MCS-, 10MCS+	13TBI, 3anoxia, 2stroke, 1other	MCS-: *M*=37 *SD*=14 ; MCS+: *M*=39 *SD*=12	4F	*M*=23.3 *SD*=28.9 R=1.5-96 months	CRS-R	fMRI	Higher connectivity was found in MCS+ compared to MCS- in the left language-related frontoparietal network, specifically between the left dorso-lateral prefrontal cortex and the left temporo-occipital fusiform cortex. MCS+ and MCS- patients are seemingly not differentiated by networks associated to auditory processing, perception of surroundings (i.e., right frontoparietal network) and internal awareness/self-mentation (i.e., default mode network), nor by inter-hemispheric integration and structural brain damage.
Bruno et al. (2012)(Bruno et al., 2012)	Retrospective cross-sectional study	27	39	13MCS-, 14MCS+	9TBI, 18NTBI	*M*=45 *SD*=16	10F	MCS-: *M*=21 *SD*=23; MCS+: *M*=19 *SD*=26 months	CRS-R	PET	Compared to MCS-, patients in MCS+ showed higher cerebral metabolism in left-sided cortical areas encompassing the language network, premotor, presupplementary motor, and sensorimotor cortices. A functional connectivity study showed that Broca's region was disconnected from the rest of the language network, mesiofrontal and cerebellar areas in MCS- compared to MCS+ patients.
Claassen et al. (2016)(Claassen et al., 2016)	Retrospective cohort study	83	/	'comatose', 'arousable', 'aware'	83 hemorrhage	*M*=57 R=46-66	58F	?	Unclear	EEG	Increasing central gamma, posterior alpha, and diffuse theta-delta oscillations differentiated patients who were arousable from those in coma. command-following was characterized by a further increase in central gamma and posterior alpha, as well as an increase in alpha permutation entropy.
Gulden-mund et al. (2016)(Guldenmund et al., 2016)	Retrospective cross-sectional study	61	28	16UWS, 8MCS-, 37 MCS+	30TBI, 31NTBI	R=16-87 UWS: *M*=49 *SD*=20; MCS-: *M*=37 *SD*=13 MCS+: *M*=42 *SD*=21	20F	R=5-3342 UWS: *M*=112 *SD*=174 MCS: *M*=792 *SD*= 1041 days	CRS-R	Structural MRI	Contrasting patients in MCS– with MCS+ and using a liberal threshold of $p = 0.01$ (uncorrected), patients in MCS+ had a more preserved left cerebral cortex, including the middle temporal gyrus, superior temporal gyrus (primary auditory cortex and Wernicke's area,) and inferior frontal gyrus (Broca's area).

Appendix I

Zheng et al. (2017)(Zheng et al., 2017)	Prospective cross-sectional	25	/	10UWS, 7MCS-, 8MCS+	17TBI, 8NTBI	*M*=39.5 *SD*=14.2 R=17-67	6F	*M*=11.8 *SD*=5.5 R=3-30 months	CRS-R	MRI (DTI – machine learning)	UWS patients displayed reduced connectivity in most thalamo-cortical circuits of interest, including frontal, temporal, and sensorimotor connections, as compared with MCS+, but showed more pulvinar-occipital connections when compared with MCS-. Moreover, MCS- exhibited significantly less thalamo-premotor and thalamo-temporal connectivity than MCS+.
DETECTION OF COVERT COMMAND-FOLLOWING AND COMMUNICATION											
Annen et al. (2018)(Annen, Blandiaux, et al., 2018)	Prospective cross-sectional study	12	PET: 34	8UWS, 4MCS-	5TBI, 6anoxia, 1hemor-rhage	*Mdn*=47.5 IQR=20 MCS-: *M*=47.5 *SD*=20 ; UWS: *M*=43.5 *SD*=25.5	5F	*Mdn*=7.5, IQR = 7.75 MCS-: *M*=7.5 *SD*=7.75 UWS: *M*=50 *SD*=30.5 months	CRS-R	EEG (ERP), PET	Commands: count the number of target apparitions, motor imagery (opening and closing the left vs. right hand). 1/12 patient showed covert command-following during the active tactile paradigm. This patient also showed a higher cerebral glucose metabolism within the language network when compared with the other patients without covert command-following but having a cerebral glucose metabolism indicative of MCS.
Bardin et al. (2011)(Bardin et al., 2011)	Prospective multiple case study	6	14	5MCS, 1LIS	5TBI, 2stroke, 2anoxia	*M*=34.3 *SD*=14.3		*M*=33.3 *SD*=22.7 months	CRS-R	fMRI	Commands: imagine yourself swimming or play tennis. Binary and multiple-choice communication. 3/6 patients (2/5 MCS and 1/1 LIS) performed the command-following task and 1/5 MCS patient showed activation in multiple choice (intentional communication?)
Bekinschtein et al. (2011)(Bekinschtein et al., 2011)	Prospective cross-sectional study	5	3	UWS	4TBI, 1mixed	*M*=29.4 *SD*=7.8 R=20-40 Mdn=30	?	*M*=10.4 *SD*=7.1 R=5-20 *Mdn*=6 months	CRS-R	EEG, fMRI	Passive listening of words vs. noise. Commands: move your left/right hand vs. to do not move your left/right hand. 5 patients, who showed word related activity, were included in a second fMRI study aimed at detecting covert command-following. 2/5 patients activated the dorsal premotor cortex contralateral to the instructed hand, consistent with movement preparation.

Bodien et al. (2017)(Bodien et al., 2017)	Prospective cohort study	10	10	1coma, 4UWS, 2MCS-, 3MCS+	10TBI	*M*=27.9 *SD*=9.1 R=18-51	4F	*M*=242.9 *SD*=586.9 R=3-1900 Mdn=10 days	CRS-R, CAP	fMRI	Commands: motor imagery (hand squeezing and tennis playing). In patients who followed commands on the CRS-R, the hand squeezing paradigm detected covert command-following in 2/3 and the tennis playing paradigm in 0/3 subjects. In patients who did not follow commands on the CRS-R, the hand squeezing paradigm detected command-following in 1/7 and the tennis playing paradigm in 2/7 subjects.
Braiman et al. (2018)(Braiman et al., 2018)	Prospective cross-sectional study	21	13	3UWS, 12MCS, 6EMCS	18TBI, 3NTBI	*Mdn*=27, IQR=9	7F	*Mdn*=64, IQR = 40 months	CRS-R	EEG, fMRI	Passive listening of personally-relevant narratives (recorded from the patients' surrogates) or Alice's Adventures in Wonderland. Commands: imagine vs. stop imagining swinging a racket with your right hand; keep/stop opening and closing your right hand. Natural speech envelope (NSE) latencies showed significant and progressive delay across diagnostic categories. Patients who could carry out fMRI-based mental imagery tasks showed no statistically significant difference in NSE latencies relative to HCS; this subgroup included patients without behavioral command-following.
Charland-Verville et al. (2014)(Charland-Verville et al., 2014)	Prospective cross-sectional study	25	/	11UWS, 14MCS	15TBI, 10NTBI	*M*=33 *SD*=13	10F	*M*=31 *SD*=27 months	CRS-R	Breathing-based "sniff controller"	Command: try to stop a music sequence by sniffing deeply through the nose cannula. 1/14 patients with MCS was able to willfully modulate his breathing pattern to answer the command on 16/19 trials (accuracy 84%). Interestingly, this patient failed to show any other motor response to command.

Chatelle et al. (2018)(Chatelle et al., 2018)	Prospective cross-sectional study	10	10	4coma, 1UWS, 4MCS, 1LIS	2TBI, 3anoxia, 4hemor-rhage, 1stroke	*M*=56.7 *SD*=12.2 *Mdn*=56 R=37-72	2F	*M*=15.7 *SD*=11.4 *Mdn*=15 R=3-38 days	CRS-R	EEG (ERP)	Commands: count the number of target apparitions, motor imagery (opening and closing the left vs. right hand). All 10 patients completed the assessment, 9 of whom required less than 1h. The HCS and LIS patient showed more consistent BCI responses than DoC patients, but overall there was no association between BCI responses and behavioral signs of consciousness. The system is feasible to deploy in the ICU and may confirm consciousness in acute LIS, but it was unreliable in acute DoC.
Claassen et al. (2019)(Claassen et al., 2019)	Prospective cohort study	104	10	56coma, 23UWS, 25MCS	15TBI, 33 anoxia 39 hemor-rhage	*M*=61 *SD*=17	46F	*Mdn*=6 R=3-10 Days	GCS, CRS-R, GOS-E	EEG	Commands: keep/stop opening the hand. 16/104 patients (15%) had brain activation detected by EEG at a median of 4 days after injury. The condition in 8/16 patients (50%) and in 23/88 patients (26%) without brain activation improved such that they were able to follow commands before discharge. At 12 months, 7/16 patients (44%) with brain activation and 12/84 patients (14%) were able to function independently for 8 hours.
Curley et al. (2018)(Curley et al., 2018)	Prospective cross-sectional study	28	15	4UWS, 17MCS, 7EMCS	18TBI, 10NTBI	*M*=31.6 R=19-56	7F	*M*=6.5 *SD*=6.1 R=0-30 years	CRS-R	EEG, fMRI	Commands: ‘tennis’ (swinging a tennis racket with one hand), ‘open/close right (left) hand’, ‘navigate’ (walking through one’s house), and ‘swim’. EEG evidence of command-following was found in 21/28 patients and all the HCS. Substantial variability was observed in the temporal and spatial characteristics of significant EEG signals among the patients in contrast to only modest variation in these domains across healthy controls. 9/21 patients with EEG evidence of command-following also demonstrated functional MRI evidence of command-following and 9 showed no behavioral evidence of a communication channel as detected by the CRS-R.

Edlow et al. (2017)(Edlow et al., 2017)	Prospective cohort study	16	16	2coma, 3UWS, 3MCS-, 4MCS+, 4PTCS	16TBI	*M*=28.9 *SD*=9.2 R=18-51	4F	*M*=9.2 *SD*=5 R=1-17 days	CRS-R, CAP, GOSE	fMRI, EEG	Passive listening of forwards language vs. backwards language and music Commands: squeezing hand. 4/16 patients, including the 3/3 UWS patients, showed cognitive-motor dissociation (CMD). Higher-order cortex motor dissociation was identified in 2 additional patients. Complete absence of responses to language, music and motor imagery was only observed in coma patients. In patients with behavioral evidence of language function, responses to language and music were more frequently observed than responses to motor imagery (62.5–80% versus 33.3–42.9%), which is similar to the HCS. Except for one patient, all patients with CMD and higher-order cortex motor dissociation recovered beyond a confusion state by 6 months.
Faugeras et al. (2012)(Faugeras et al., 2012)	Prospective cross-sectional study	49	10	24UWS, 28MCS, 13 conscious	35% anoxia, 28% hemor-rhage, 18% TBI, 18% other	*M*=47.5 *SD*=17.4 R=16-83	17F	*M*=203 *SD*=591 *Mdn*= 35 R=6-2555 days	CRS-R	EEG	Mismatch negativity (MMN) with local and global deviants, command: to count the stimuli. 6/24 UWS and 9/28 MCS recordings showed local MMN; 2/24 UWS and 4/28 MCS showed global MMN in counting condition. The ERP "global effect" can be used as a highly specific marker of consciousness in non-communicating patients with a specificity close to 100%.
Fernandez-Espejo et al. (2015)(Fernández-Espejo et al., 2015)	Multiple case study	2	15	1UWS, 1EMCS	2TBI	38 49	1F	149 146 months	CRS-R	fMRI, DTI	Commands: move the right hand to hit a tennis ball vs. imagine the same movement In contrast to mental imagery, motor execution was associated with an excitatory coupling between the thalamus and primary motor cortex. A selective structural disruption in the fibers connecting these 2 regions was detected in the UWS patient but not in the EMCS patient.

Forgacs et al. (2014)(Forgacs et al., 2014)	Prospective cohort study	44	/	8UWS, 36MCS/ EMCS	28TBI, 6anoxia, 6stroke, 1mixed, 3other	*M*=32 R=16-57	13F	*M*=78 R=6-312 months	CRS, CRS-R or medical exam	EEG, PET, fMRI	Commands: imagine vs. stop imagining yourself swimming All 4 patients with fMRI evidence of covert command-following consistently demonstrated well-organized EEG background during wakefulness, spindling activity during sleep, and relative preservation of cortical metabolic activity.
Forgacs et al. (2016)(Forgacs, Fridman, Goldfine, & Schiff, 2016)	Single case study	1	PET: 10	MCS	Anoxia	± 20	F	33 months	CRS-R	EEG, PET	Commands: keep opening and closing the hand vs. stop opening and closing the hand Using quantitative EEG, the patient showed evidence for willful modulation of brain activity in response to auditory commands revealing covert consciousness. Resting neuronal metabolism and electrical activity across the entire anterior forebrain was found to be normal despite severe structural injuries to primary motor, parietal, and occipital cortices.
Gibson et al. (2016)(Gibson et al., 2016)	Prospective cross-sectional study	14	15	7UWS, 4MCS, 2EMCS, 1LIS	6TBI, 4anoxia, 4other	*M*=40.8 *SD*=12.3 R=19-58	7F	*M*=7.8 *SD*=6.7 R=0.9-20.4 years	CRS-R	EEG (ERP), fMRI	1) Somatosensory Selective Attention Paradigm (EEG): count the vibrations presented only to the target wrist. 2) Mental Imagery Paradigm (fMRI): imagine swinging the right arm to hit a tennis ball/walking from room to room in their house and visualize all objects they would encounter. 3) Auditory Selective Attention Paradigm (fMRI): count a target word ("yes" or "no") presented among pseudorandom - 9 -apillary- 9 -s vs. relax. 6/14 patients produced only sensory responses, with no evidence of cognitive ERPs whereas 8/14 patients demonstrated reliable bottom-up attention-orienting responses (P3a). No patient showed evidence of top-down attention (P3b). Only those patients, who followed commands, whether overtly with behavior or covertly with fMRI, also demonstrated ERP evidence of attentional orienting.

Goldfine et al. (2011)(Goldfine et al., 2011)	Prospective multiple case study	3	5	2MCS, 1LIS	2TBI, 1stroke	25, 19, 24	?	25, 30 (then 10), 31 (then 43) months	?	EEG	Commands: imagine yourself swimming or stop imagining yourself swimming. 1/2 MCS and 1/1 LIS showed evidence of motor imagery task performance, though with patterns of spectral change different from the controls. EEG power spectral analysis can be used as a flexible bedside tool to demonstrate awareness in brain-injured patients.
Guger et al. (2018)(Guger et al., 2018)	Prospective cross-sectional study	12	3	UWS	4TBI, 2stroke, 4anoxia, 2other	*Mdn*=53.3 R=19-91	3F	*Mdn*=2 R=1-28 months	CRS-R	EEG	Two paradigms: 'VT2' with 2 vibro-tactile stimulators fixed on the patient's left and right wrists and 'VT3' with 3 vibro-tactile stimulators fixed on both wrists and on the back. Commands: mentally count either the stimuli on the left or right wrist. 2/12 patients achieved VT3 80% accuracy and went through communication testing. 1/12 of these patients answered 4/5 questions correctly in session 1, whereas the other patient answered 6/10 and 7/10 questions correctly in sessions 2 and 4.
Habbal et al. (2014)(Habbal et al., 2014)	Prospective cross-sectional study	38	18	10UWS, 8MCS-, 20MCS+	23TBI, 15NTBI	*M*=39 *SD*=14	18F	25 patients: R=1.08–11.83 years 13 patients: R=51–347 days	CRS-R	EMG	Commands: to move the hand or the leg, to clench the teeth, vs. control auditory phrase ("It is a sunny day"). EMG activity was higher solely for the target command in one patient in permanent UWS and in three patients in MCS+.

Hauger et al. (2015)(Solveig L. Hauger et al., 2015)	Prospective cross-sectional study	20	20	11MCS-, 9MCS+	13TBI, 3anoxia, 2stroke, 2other	*M*=39.7 *SD*=14.2 R=19-66	9F	*M*=32.7 *SD*=35.3 R=3.6-117 months	CRS-R	EEG (ERP)	1) Task 1: Passive listening of 100x SON vs. 100x SON with command "Listen for change in pitch"; 2) Task 2: Passive listening of 50x SON/50x unfamiliar name vs. 50x SON/50x unfamiliar name with command "Count your name". 4/20 patients (3MCS+/1MCS−) showed a larger P3 component in the active compared to the passive condition of task 1. Here, 6/9 MCS+ patients failed to be detected in task 1, rendering a false negativity rate of 67%, while 1/11 MCS− patient was considered a responder in this task. 9/20 patients (4MCS+/5MCS−) showed higher P3 amplitudes in the active counting condition compared to the passive listening in task 2. Here, 5/9 MCS+ patients did not display elevated P3 responses in the counting condition (false negative rate of 56%). Yet, 5/11 MCS− patients were considered responders in this task. With regard to the ability of ERP to distinguish between MCS+ and MCS−, sensitivity was 67%, with 3 MCS+ patients not displaying clear EEG evidence of command-following.
Hinterberger et al. (2005)(Hinterberger et al., 2005)	Prospective cross-sectional study	5	5	UWS	?	*M*=47 *SD*=14 R=19-70	?	?	None	EEG	Semantic oddball (SON), word matching (pair of words semantically linked or not) and semantic congruence (sentences) tasks. Commands: imagine a left or right hand movement according to the verbal requirement. 3/5 patients showed significant N100 for the semantic oddball paradigm. 1/5 patient differed in his responses between meaningful and meaningless words but not with the typical shape of the N400. 2/5 patients showing the highest responsiveness were selected for specific Thought and Translation Device (TTD) training.

Höller et al. (2013)(Höller et al., 2013)	Prospective cross-sectional study	14	22	9UWS, 5MCS	4TBI, 3anoxia, 5hemor-rhage, 2other	*M*=51.2 *SD*=14.1 R=31-73	6F	*M*=21.1 *SD*=32.6 R=2-119	CRS-R, WHIM	EEG	Commands: moving both hands or hold both hands vs. rest condition: hold the hands firm. In healthy participants, coherence involved mainly frontal regions and the best classification tool was support vector machines (SVM). 5/14 patients had at least one feature-classifier outcome with $p<0.05$ (none of which were coherence or power spectra), though none remained significant after false discovery rate correction for multiple comparisons. The present work suggests the use of coherences in DoC patients.
Liang et al. (2014)(Liang et al., 2014)	Prospective cross-sectional study	5	11	?	4TBI, 1 unclear	*M*=42,8 *SD*=14,6 R=24-60	2F	*M*=46.6 *SD*=40.2 *Mdn*=34 R=14-118 months	GCS, GOS, WHIM	fMRI	Passive listening of sentences (low vs. high ambiguity) and signal correlated noise. Commands: imagine navigating your home/playing tennis, imagine familiar faces, count up from 10 by 7's). For all patients, no significant and meaningful activations were found for the speech comprehension test. 2/5 patients showed covert command-following.
Lulé et al. (2013)(Lulé et al., 2013)	Prospective cross-sectional study	18	16	3UWS, 13MCS, 2LIS	UWS: 2anoxia MCS: 5TBI	UWS: *M*=61 *SD*=17 ; MCS: *M*=42 *SD*=21	UWS: 1F MCS: 4F	UWS: *M*=10 *SD*=15 ; MCS: *M*=70 *SD*=109 months	CRS-R	EEG	4-choice auditory oddball using 4 stimuli ("yes", "no", "stop", "go") and command: to count the number of times a target ("yes" or "no") is presented. Command-following in 1/13 MCS and 1/2 LIS patients, communication in 1/2 LIS patient only.
Monti et al. (2009)(Monti et al., 2009)	Prospective single case study	1	12	MCS+	Anoxia	?	?	?	CRS-R	fMRI	Passive listening of repeated monosyllabic words (blocks of 26 words). Commands: detect and count targets. In 1 MCS patient and HCS, the counting task revealed a fronto-parietal network previously associated with target detection and working memory. Furthermore, the activity in these regions appeared highly synchronous to the onset and offset of the counting blocks.

Monti et al. (2013)(Monti et al., 2013)	Prospective single case study	1	13	MCS-	TBI	?	0F	18 months	CRS-R	fMRI	Commands: look at the face vs. the house (visual recognition). This approach revealed appropriate brain activations, undistinguishable from those seen in healthy and aware volunteers. The patient was able to focus one of two competing stimuli, and switch between them on command.
Naci et al. (2013)(Naci & Owen, 2013)	Prospective multiple case study	3	15	1UWS, 2MCS	2TBI, 1anoxia	34 25 38	0F	184 67 147 (then 152) months	CRS-R	fMRI	Passive listening of single words and 4 sentences (questions). Commands: count target words. 3/3 patients demonstrated command-following according to instructions. 2/3 patients (1MCS and 1UWS) were also able to guide their attention to repeatedly communicate correct answers to binary questions.
Owen et al. (2006)(A M Owen et al., 2006)	Prospective single case study	1	12	UWS	TBI	23	1F	5 months	WHIM	fMRI	Passive listening of sentences versus acoustically matched noise, and ambiguous versus non ambiguous sentences. Commands: tennis and spatial navigation imagery. Speech-specific activity in bilateral middle and superior temporal gyri, and additional response in left inferior frontal area in response to ambiguous sentences. Supplementary motor area activation to tennis imagery and in parahippocampal gyrus, posterior parietal lobe and lateral premotor cortex in response to spatial navigation imagery.
Pan et al. (2014)(Pan et al., 2014)	Prospective cross-sectional study	8	4	4UWS, 3MCS, 1LIS	3TBI, 3anoxia, 2stroke	*M*=38 *SD*=19 R=16-70	4F	*M*=10.2 *SD*=11.9 R=1-37 months	CRS-R	EEG (SSVEP and P300)	Commands: focus on the familiar/unfamiliar photo and count the flashes of the corresponding photo frame. Four HCS, 1/4 UWS, 1/3 MCS, and the LIS patient were able to selectively attend to their own or the unfamiliar photos (classification accuracy, 66–100%). Two additional patients (1UWS and 1MCS) failed to attend the unfamiliar photo (50–52%) but achieved significant accuracies for their own photo (64–68%).

Risetti et al. (2013)(Risetti et al., 2013)	Prospective cohort study	11	/	8UWS, 3MCS	4TBI, 6stroke, 1anoxia	*M*=38.3 *SD*=15.1 R=20-63	5F	*M*=8.6 *SD*=5.6 R=3-19.5 months	CRS-R	EEG	Passive listening of sounds (standards, deviants) and SON. Command: count the novel stimuli. 10/11 patients showed ERP components such as mismatch negativity (MMN) and novelty P300 (nP3) under passive condition. In the active condition, the nP3 component displayed a significant increase in amplitude and a wider topographical distribution with respect to the passive listening, only in MCS. In 2/4 patients who underwent a second recording session consistently with their transition from UWS to MCS, the nP3 component elicited by passive listening of SON stimuli revealed a significant amplitude increment. The amplitude of the nP3 component in the active condition, acquired in each patient and in all recording sessions, displayed a significant positive correlation with the total scores and with the auditory sub-scores of the CRS-R administered before each EEG recording.
Rodriguez-Moreno et al. (2010)(Rodriguez Moreno et al., 2010)	Prospective cross-sectional study	10	/	3UWS, 5MCS, 1EMCS, 1LIS	5TBI, 1anoxia, 3stroke, 1other	*M*=34.4 *SD*=15.9 R=18-58	5F	*M*=20.5 *SD*=25.2 R=2-84 months	CRS-R	fMRI	Silent picture naming task (using drawings of objects from the Boston Naming Set 2) also assessing command-following capacity. The LIS and EMCS patients engaged a complete network of essential language-related regions during the object-naming task. 5/5 MCS and 2/3 UWS patients demonstrated both complete and partial preservation of the object-naming system. fMRI during object naming can elicit brain activations in DoC patients similar to those observed in HCS during command-following, and patients can be stratified by completeness of the engaged neural system.

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Vassilieva et al. (2019)(Vassilieva et al., 2019)	Prospective cross-sectional study	48	20	41 neurological patients, 1MCS-, 1EMCS, 5 sedated-comatose	2TBI, 5stroke, 3hemorrhage, 38other	*Mdn*(IQR) : 60.5(51-68) ; 50(41-70) ; 34(34-34) ; 62(55-64)	31F	?	None (standard neurological bedside examination)	Automated pupillometry	Commands: mentally calculate arithmetic problems. 14/ 20 (70%) HCS and 17/43 (39.5%) neurological patients, including 1 in the ICU, fulfilled pre-specified criteria for command-following by showing - 15 - apillary dilations during 4 of 5 arithmetic tasks.
CORTICAL ACTIVITY RELATED TO AUDITORY/SPEECH PROCESSING											
Balconi et al. (2015)(Balconi & Arangio, 2015)	Prospective cross-sectional study	18	/	7UWS, 11MCS	6TBI, 9anoxia, 3stroke	*M*=49.5 *SD*=11.7 R=25-64	10F	*M*=48 R=6-63 months for initial sample of 22patients	CNC, DRS	EEG (ERP, N400)	Passive listening of word sequences with related (congruent) vs. unrelated (incongruent) final words. Increased N400 peak amplitude within the fronto-central cortical areas was revealed in response to incongruous sequences for all patients. Moreover, this peak was temporally delayed in response to incongruous conditions in these cortical sites. In addition, UWS patients showed a delayed N400 in comparison with MCS patients in incongruous condition. A direct correlation was found between the clinical scales and the ERP modulation, in terms of peak amplitude and latency.
Balconi et al. (2013)(Balconi et al., 2013)	Prospective cross-sectional study	18	20	10UWS, 8MCS	5TBI, 10 anoxia, 3stroke	*M*=50 *SD*=10.11 R=25-69	8F	*M*=52 R=6-70 months	CNC, DRS, GCS	EEG (ERP, N400)	Passive listening of congruous vs. incongruous four-word sequences. Increased N400 peak amplitude within the fronto-central cortical areas was shown in response to incongruous sequences for both patients and HCS. Delayed peak was also observed within the frontal sites for patients in the incongruous condition as compared with HCS subjects. MCS and mainly UWS diagnosis was not accompanied by the abolition or reduction of the ERP N400 component.

Beukema et al. (2016)(Beukema et al., 2016)	Prospective cross-sectional study	16	17	8UWS, 8MCS	8TBI, 8NTBI	*M*=38.5 *SD*=17.2 R=16-69	4F	*M*=42.8 *SD*=50.8 R=5-202 months	CRS-R	EEG (ERP)	Passive listening vs. command-following (think if related or unrelated word) of 400 words (100 related word pairs, 100 unrelated word pairs). 7/16 (44%) patients exhibited markers of the differential processing of speech and noise and 1/16 patient produced evidence of the semantic processing of speech (i.e. the N400 effect). There were no differences in auditory processing between UWS and MCS patient groups.
Coleman et al. (2007)(M. R. Coleman et al., 2007)	Cross-sectional study	14	/	7VS 5MCS 2EMCS	7TBI 3anoxia 4stroke	*M*=42.9 *SD*=15.0 R=22-67	5F	*M*=26.5 *SD*=39.4	GCS, CRS-R	fMRI	Passive listening of intelligible speech vs. unintelligible noise, and low vs. high ambiguity sentences. This study is preliminary to Coleman et al. (2009).(Martin R. Coleman et al., 2009) It used the same methodology on a reduced sample.
Coleman et al. (2009)(M. R. Coleman et al., 2009)	Prospective single case study	1	?	MCS-	TBI	19	M	7 months	CRS-R, SMART	EEG, fMRI, DTI, behavioral	Passive listening of speech (ambiguous vs. unambiguous) vs. noise. Commands: tennis playing or navigating, face versus house recognition. EEG confirmed that he retained a preserved neural axis supporting vision and hearing, and suggested some evidence that he was able to create a basic memory trace. A hierarchical fMRI auditory paradigm suggested perception of sound and speech, but no evidence of speech comprehension or ability to respond to command. This was corroborated in the visual modality using a hierarchical paradigm demonstrating that he was able to perceive motion, objects and faces, but retained no evidence of being able to respond to command.

Coleman et al. (2009)(Martin R. Coleman et al., 2009)	Prospective cohort study	41	/	22UWS, 19MCS	26TBI, 11 anoxia, 4stroke	*M*=40 R=17–68	13F	*M*=17.9 *SD*=26.2 R=2-122 months	CRS-R, SMART	fMRI	Passive listening of intelligible speech vs. noise, high vs. low ambiguity sentences. 2 UWS patients did in fact demonstrate neural correlates of speech comprehension when assessed using fMRI The level of auditory processing revealed by fMRI correlated strongly with the patient's subsequent behavioral recovery, 6 months after the scan.
Crivelli et al. (2019)(Crivelli et al., 2019)	Prospective cross-sectional study	21	/	21UWS	6TBI, 8stroke, 7anoxia	*M*=59.1 *SD*=9.1 R=29-86	8F	*M*=37.2 *SD*=29.9 R=12-117 months	CNC, DRS	EEG, physiological measures	Passive listening of SON vs. other names. Analysis of EEG, skin conductance and heart rate modulations highlighted a consistent pattern of increased skin conductance and heart rate measures in response to SON with respect to other names. Increased delta and decreased alpha activity was observed over frontal areas in response to SON with respect to other names.
Erlbeck et al. (2017)(Erlbeck et al., 2017)	Prospective cohort study	19	45 to rate the relation of word-pairs	13UWS, 3MCS, 3EMCS	3TBI, 10 anoxia, 3stroke, 2other	*M*=50.7 *SD*=13.7 R=31-69	8F	*M*=72.3 *SD*=39.8 R=3-141 months	CRS-R	EEG (ERP, N400)	Passive listening of word pairs (related vs. unrelated) and short sentences (correct vs. incorrect ending word). 15/19 patients did not show any response to the stimulation. In the mismatch negativity (MMN) paradigm, an MMN was identified in 2/19 patients; in the N400 words paradigm, only an N1 was identified in 1/19 patient; and in the N400 sentences paradigm, a late positive complex (LPC) was identified in 2/19 patients.
Fernández-Espejo et al. (2010)(Fernández-Espejo et al., 2010)	Prospective single case study	1	19 for DTI	UWS	TBI	48	0F	33 days (then 7 months)	GCS, DRS, LCFS, BDAE	DTI, fMRI, behavioral	Passive listening of forward vs. backward speech (20 second long spoken narratives regarding everyday events). The fMRI analysis revealed anatomically appropriate activation to speech in both the 1st and the 2nd scans but a reduced pattern of task-induced deactivations in the 1st scan. DTI analysis revealed relative preservation of the arcuate fasciculus and of the global normal-appearing white matter at both time points. The neuropsychological assessment revealed recovery of receptive linguistic functioning by 12-months post-ictus.

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Formisano et al. (2019)(Formisano et al., 2019)	Retrospective cohort study	15	10	7UWS, 3MCS-, 5MCS+	7TBI, 1anoxia, 7stroke	*M*=50 *SD*=16.4 R=25-73	5F	*M*=123.1 *SD*=32 R=66-189 days	CRS-R, GCS, neuro-psycho-logical testing for aphasia	EEG (ERP), behavioral	Passive listening of 100 sentences with the last word semantically incongruent vs. congruent. The N400 ERP component with centro-parietal topography was found in 9/10 HCS in response to the ill-formed sentences. A significant N400 component could be detected in 64% (9/ 14 patients); no significant N400 ERP component was retrospectively detected in those EMCS patients who showed aphasia at the follow-up; and the presence/absence of the N400-ERP component was consistent with the brain lesion side and significantly predict the recovery.
Kempny et al. (2018)(Kempny et al., 2018)	Prospective cross-sectional study	16	12	5UWS, 11MCS	4TBI, 5anoxia, 6stroke, 1other	*M*=46 *SD*=11 R=18-68	6F	*M*=17.3 *SD*=22.6 R=1.8-80.9 months	SMART	EEG (ERP)	Passive listening of SON, reversed name, other's names. In 4 DoC patients (3MCS and 1UWS) was detected a statistically significant difference in EEG response to SON vs other peoples' names with ERP latencies (~300 ms and ~700 ms post stimuli).
Kotchoubey et al. (2005)(B. Kotchoubey et al., 2005)	Prospective cohort study	98	22	50UWS, 34MCS, 4unclear, 10 severely brain-damaged conscious patients	36TBI, 27 anoxia, 32 hemor-rhage, 3other	*M*=44 R=15-76	27F	*M*=8.7 R=1.2-127 months	DRS	EEG (ERP)	Semantic oddball tasks: 100 monosyllabic word pairs semantically related vs. unrelated, 100 seven-word sentences (passive listening with last word congruent vs. incongruent) + commands: e.g., count the animal names. Cortical responses were found in all UWS patients with a background EEG activity >4 Hz. All responses investigated, including those to semantic stimuli that indicated comprehension of meaning, occurred significantly above chance, though less frequently than in patients with severe brain injuries who were conscious. In a subpopulation of UWS patients with preserved thalamocortical feedback connections, remaining cortical information processing is a consistent finding and may even involve semantic levels of processing.

Kotchoubey et al. (2009)(Boris Kotchoubey et al., 2009)	Cross-sectional study	30	16	15UWS, 12MCS, 3LIS	10TBI, 7hemor-rhage, 3stroke, 7anoxia, 3other	*M*=43 *SD*=15 R=18-68	9F	*M*=19.1 *SD*=29.6 R=1,5-108 months	None	EEG (ERP), MEG	Passive listening of emotional vocalizations (exclamations of joy e.g. "heey!" vs. single exclamation of woe: "oooh!" deviant). Significant differences between emotionally positive and negative stimuli were found in 6/27 DoC patients. No difference in significant responses to prosody was found between UWS vs. MCS patients, between TBI vs. NTBI patients, or between those with disease duration <10 months vs. >10 months.
Kotchoubey et al. (2014)(Boris Kotchoubey et al., 2013)	Prospective cross-sectional study	55	21	29UWS, 26MCS	14TBI, 23 anoxia, 11 hemor-rhage, 7other	*M*=48.6 *SD*=15 R=16-73	23F	*M*=25.9 *SD*=33.9 R=1-132 months	CRS-R	fMRI	Passive listening of factually correct vs. incorrect short sentences. In the contrast "incorrect-minus-correct" significant activations in the relevant brain regions were obtained in 17/21 HCS and in 16/55 patients. The 16 responder patients had a significantly longer time since accident than the 39 non-responders. Responders and non-responders did not differ in terms of the diagnosis (UWS vs. MCS), age, CRS-R score, or the degree of brain atrophy.
Laureys et al. (2004)(S Laureys et al., 2004)	Prospective single case study	1	/	MCS	Intra-cerebral hemorrh age	42	0F	6 months	WHIM, CRS-R, WNSSP	EEG (ERP), PET	Passive listening of frequency-modulated noise, infant cries and SON. Auditory stimuli with emotional valence (infant cries and the SON) induced a much more widespread activation than did meaningless noise; the activation pattern was comparable with that previously obtained in HCS.
Lechinger et al. (2016)(Lechinger et al., 2016)	Prospective cross-sectional study	15	24	8UWS, 7MCS	3TBI, 5anoxia, 4hema-toma, 1hemor-rhage, 2other	*M*=47.8 R=20-73) UWS: *M*=48.13 *SD*=11.24 MCS: *M*=47.43 *SD*=16.19	5F	*M*=70.7 *SD*=52 R=8-152 months	CRS-R	EEG (ERP)	Passive listening of first names including SON. DoC patients did not show clear stimulus-specific processing. General reactivity toward any auditory input, however, allowed for a reliable differentiation between MCS and UWS patients.

Li et al. (2018)(Li et al., 2018)	Prospective cross-sectional study	19	/	10UWS, 9MCS	?	UWS: *M*=51.1 *SD*=10.2 MCS: *M*=39.3 *SD*=11.9	4F	UWS: *M*=4.05 *SD*=1.38 MCS: *M*=3.10 *SD*=1.92 months	CRS-R, GCS	EEG (ERP)	Passive listening of music vs. SON + reaction to habit stimulation (i.e., wiping alcohol on the lips for alcoholic patients or introducing the smell of cigarette smoke for smoking patients). The highest degree of EEG response was from the call name stimulation, followed by habit and music stimulations. Significant differences in EEG wavelet energy and response coefficient were found both between habit and music stimulation, and between habit and call-name stimulation.
Naci et al. (2018)(Naci et al., 2018)	Prospective cross-sectional study	11	16	6UWS, 4MCS, 1LIS	5TBI, 4anoxia, 2other	*M*=37.4 *SD*=12.9 R=19-55	6F	*M*=84.7 *SD*=87.6 R=3-248 months	CRS-R	fMRI	Passive listening of plot-driven auditory narrative from the kidnapping scene of the movie "Taken" (5 minutes) + commands: count target words. The DoC+ (covertly aware) group showed a significant down-regulation of the auditory and fronto-parietal networks connectivity in the audio story relative to the resting state (auditory-dorsal attention and executive control networks), and was significantly different from the DoC- group, who did not show this effect. The DoC- group showed significantly enhanced auditory-dorsal attention network connectivity during the audio story relative to resting state.

Nigri et al. (2017)(Nigri et al., 2017)	Prospective cross-sectional study	11	18	4UWS, 7MCS	4TBI, 2anoxia, 5hemor-rhage	*M*=50.6 *SD*=17 *Mdn*=57 R=19–69	7F	*M*=63.4 *SD*=81.7 *Mdn*=27 R=5–252 months	CRS-R	fMRI, EEG, PET	Passive listening of pairs of semantically related vs. unrelated words + pairs of words vs. pseudowords (lexical and semantic priming). Significant BOLD signal changes were detected not only in 4/7 MCS patients (n = 4), but also in 4/4 UWS patients. Clinical scores were positively correlated with BOLD signal changes extracted in auditory cortex during some linguistic conditions. Using a hierarchical design, the authors were able to separate low level auditory linguistic activations (LLA) (independent from the lexical or semantic nature of the stimuli) from the effects possibly related to listening real words. In line with their expectations, all the patients, except one, showing any activation in upper levels (7/11), presented BOLD signal changes for this low-level contrast (LLA). 3 MCS patients with no evidence of fMRI activation showed a very low score for the auditory subscale of CRS-R (score 1), while another MCS patient, who showed a unilateral cluster of activation in the left STG, presented a higher score in the same subscale (score 2).
Owen et al. (2005)(A. Owen et al., 2005)	Longitudinal prospective single case study	1	/	UWS	Ictus	30	0F	4 then 9 months	None	PET, fMRI	Passive listening of sentences of high, medium or low intelligibility (PET) and high- and low-ambiguity sentences (fMRI). PET revealed preserved and consistent responses in predicted regions of auditory cortex in response to intelligible speech stimuli. A preliminary fMRI examination at the time of the second session revealed partially intact responses to semantically ambiguous stimuli, which are known to tap higher aspects of speech comprehension.
Perrin et al. (2006)(Perrin et al., 2006)	Prospective cross-sectional study	15	5	5UWS, 6MCS, 4LIS	4TBI, 11NTBI	*M*=54.9 *SD*=17.2 R=24-83	3F	*M*=14.1 *SD*=25.6 R=0.4-84 months	CRS-R, GLS	EEG (ERP)	Passive listening of SON vs. other names. A P3 component was observed in response to the SON in all LIS patients, in all MCS patients, and in 3 of 5 UWS patients. P3 latency was significantly delayed for MCS and UWS patients compared with HCS.

Rohaut et al. (2015)(Rohaut et al., 2015)	Prospective cohort study	29	19	15UWS, 14MCS	7TBI, 8anoxia, 9stroke, 5other	*M*=44.4 *SD*=15.3 R=18-78	9F	*M*=159 *SD*=365 R=7-1593 days	FOUR, GCS, CRS-R, GOSE	EEG (ERP)	Passive listening of 68 pairs of semantically related words (congruent, semantic priming) vs. 68 pairs of unrelated words (incongruent). There was a large variability in latencies for both N400 and LPC in HCS (N400 in 8/19 and LPC in 8/19). N400 effect was found in 6/29 DoC patients (5/14 MCS; 1/15 UWS) and LPC response in 9/29 DoC patients (8/14 MCS; 1/15 UWS). Whereas N400-like ERP components could be observed in the UWS, MCS and conscious groups, only MCS and conscious groups showed a LPC response, suggesting that this late effect could be a potential specific marker of conscious semantic processing. The only 3 patients presenting both significant N400 and LPC effects were MCS, and 2 of them regained consciousness and functional language abilities.
Schabus et al. (2011)(Schabus et al., 2011)	Prospective cross-sectional study	14	14	10UWS, 4MCS	7TBI, 3anoxia, 3stroke, 1other	R=20-73 UWS: *M*=44.10 *SD*=12.32; MCS: *M*=52.25 *SD*=17.8	6F, 8M	*M*=78.1 *SD*=49.3 R=8-152 months	CRS-R	EEG (ERP)	Passive listening of sentences such as “the opposite of black is… white/yellow/nice” (i.e., 3 conditions: target vs. unrelated word vs. antonym). Only MCS but not UWS patients show differential processing of unrelated (“nice”) and antonym (“white”) words in the form of parietal alpha (10-12Hz) event-related synchronization and desynchronization (ERS/ERD), respectively.

Schiff et al. (2005)(N D Schiff et al., 2005)	Prospective multiple case study	2	7	MCS	1TBI, 1stroke	21 33	0F	18 24 months	?	fMRI	Passive listening of auditory narratives of familiar events presented by a familiar person (forward and backward) + tactile stimulation (light touch of both hands). In the case of the patient language-related tasks, auditory stimulation with personalized narratives elicited cortical activity in the superior and middle temporal gyrus. The HCS imaged during comparable passive language stimulation demonstrated responses similar to the patients' responses. However, when the narratives were presented as a time-reversed signal (without linguistic content), the MCS patients demonstrated markedly reduced responses as compared with HCS.
Schnakers et al. (2015)(Schnakers et al., 2015)	Prospective cross-sectional study	26	14	10UWS, 8MCS-, 8MCS+	9TBI, 12 anoxia, 3stroke, 2other	*M*=38 *SD*=12 R=18-68	8F	*M*=39.9 *SD*=36.5 R=0.47-124.8 months	CRS-R	EEG (ERP)	Passive listening of SON repeated 100x over 4 consecutive blocks Command: listen carefully for pitch change. In 5/8 MCS+ patients as well as in 3/8 MCS− patients and 1/10 UWS patient, an enhanced P3 amplitude was observed in the active vs. passive condition. Relative to HCS, patients showed a response that was (1) widely distributed over frontoparietal areas and (2) not present in all blocks. The amplitude of the response was lower in fronto-central electrodes compared with HCS but did not differ from that in the MCS+ group.

Schoenle et al. (2004)(Schoenle & Witzke, 2004)	Cross-sectional study	120	?	35.8% vegetative state, 19.2% 'near vegetative state', 45% 'not vegetative state'	41.7% TBI, 25.8% anoxia, 32.5% stroke	*M*=44.2 *SD*=14.7 R=18-75	30%F	?	?	EEG (ERP, N400)	Passive listening of sentences with semantically incorrect or correct final word. Patients who were not in vegetative state (NOVS) produced the most robust results on N-400 testing. Only 9.23% of patients in NOVS did not show a N-400, while 90.17% were able to distinguish semantically correct from semantically anomalous sentences. Patients in near vegetative state (NEVS) exhibited no N-400 in 23.26% of cases. However, 76.74% produced a N-400 in one of the 3 forms. While vegetative state patients were lacking a N-400 in 61.12% of all cases, 11.96% of this patient group exhibited distinct semantic capabilities and 26.91% showed "emerging" N-400 waves. In total, 38.87% of vegetative state patients showed some form of N-400 waves, implying that semantic capacities existed.
Sergent et al. (2017)(Sergent et al., 2017)	Prospective cross-sectional study	13	15	4UWS, 8MCS, 1EMCS	6TBI, 6stroke, 1anoxia	*M*=46.1 *SD*=14.6 R=25-63	3F	*M*=19.6 *SD*=29.7 R=0.5-96 months	CRS-R	EEG (ERP)	Passive listening of SON, other name and non-vocal control matched to the SON. A significant P300 was observed in most but not all HCS (9/15). This effect was present in 4/8 MCS patients, and 1/4 UWS patients and absent in the conscious patient.
Staffen et al. (2006)(Staffen et al., 2006)	Prospective single case study	1	3	UWS	Anoxia	50	0F	?	?	fMRI	Passive listening of phrase containing SON or other name. The patient showed higher brain activity during hearing his own name than another name in the bilateral medial prefrontal cortex. The same effect was also observed in the left temporo-parietal and superior frontal cortex, although only at an uncorrected significance level of $p<0.005$.

Steppacher et al. (2013)(Steppacher et al., 2013)	Prospective longitudinal cohort study	92	/	53UWS, 39MCS	43TBI, 25 anoxia, 24other	UWS: *M*=44.5 *SD*=14.5; MCS: *M*=45.0 *SD*=16.9	28F, 65M	UWS: *M*=1.9 *SD*=1.6 MCS: *M*=6.8 *SD*=8.5 months	Coma Remis-sion Scale, Barthel	EEG (ERP, N400)	Passive listening of five-word sentences with semantically incorrect or correct final word. Within the 1st year of the disease, many patients showed an intact P300 and several also an N400, indicating considerable residual information processing. At clinical follow-up, about 25% of the patients recovered and regained communicative capabilities. A highly significant relationship between N400, but not P300, presence and subsequent recovery was found. Specifically the N400 ERP is suggested as an important tool to assess information-processing capacities that can predict the likelihood of recovery of patients in UWS or MCS.
Tomaiuolo et al. (2016)(Tomaiuolo et al., 2016)	Longitudinal prospective case study	1	/	From UWS to EMCS	TBI	23	0F	?	CRS-R	fMRI	Passive listening of forward vs. backward speech (narratives). The patient progressed from an UWS to a MCS and his task-related neural responses mirrored the clinical change. Specifically, while in an MCS, but not a UWS, the patient showed a selective recruitment of the left angular gyrus when he listened to a native speech narrative, as compared to the reverse presentation of the same stimulus. Furthermore, the patient showed an increased response in the language-related brain network and a greater deactivation in the default mode network following his progression to an MCS.
Wu et al. (2011)(Wu et al., 2011)	Prospective cohort study	37	30	21UWS, 16MCS	32TBI, 5NTBI	R=19-80 UWS: *M*=46.9 *SD*=17.5 MCS: *M*=45.7 *SD*=10.1	10F, 27M	UWS: *M*=92.9 *SD*=46.4 MCS: *M*=106.6 *SD*=51.7 days	GCS, Rappa-port Coma/ Near-Coma Scale, CRS-R	EEG	Passive listening of commonly used words (e.g., ‘day’, ‘country’ and ‘ticket’) and music (popular song) + painful stimuli on each side of the legs. The UWS subjects had the lowest nonlinear indices followed by the MCS subjects and the control group had the highest. Both patient groups had poorer response to auditory and painful stimuli than the control group.

Appendix I

Supplementary material 4: Quality assessment of the studies included in the systematic review

REFERENCES	RISK OF BIAS				APPLICABILITY		
	POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
BEDSIDE LANGUAGE BEHAVIORAL ASSESSMENTS							
Aubinet et al. (2018)(Aubinet, Murphy, et al., 2018)	+	?	?	?	-	-	-
Borer-Alafi et al. (2004)(Borer-Alafi et al., 2002)	+	?	+	?	+	-	+
Cheng et al. (2013)(Cheng et al., 2013)	+	?	?	?	-	-	-
Day et al. (2018)(Day et al., 2018)	+	?	?	+	-	-	-
Rasmus et al. (2019)(Rasmus et al., 2019)	+	?	+	?	+	-	+
Yamaki et al. (2018)(Yamaki et al., 2018)	+	?	?	?	-	-	-
NEURAL CORRELATES OF THE MCS LANGAGE-RELATED SUB-CATEGORIZATION							
Aubinet et al. (2019)	+	+	?	-	-	-	-
Aubinet et al. (2019)(Aubinet et al., 2019)	+	+	?	?	-	-	-
Aubinet et al. (2018)(Aubinet, Larroque, et al., 2018)	+	+	?	?	-	-	-
Bruno et al. (2012)(Bruno et al., 2012)	+	+	?	-	-	-	-
Claassen et al. (2016)(Claassen et al., 2016)	+	?	?	?	-	-	-
Guldenmund et al. (2016)(Guldenmund et al., 2016)	+	+	?	?	-	-	-
Zheng et al. (2017)(Zheng et al., 2017)	+	+	?	+	-	-	-
DETECTION OF COVERT COMMAND-FOLLOWING AND COMMUNICATION							
Annen et al. (2018)	+	?	?	?	-	-	-
Bardin et al. (2011)(Bardin et al., 2011)	+	?	?	?	-	-	-
Bekinschtein et al. (2011)	+	?	-	?	-	-	-
Bodien et al. (2017)	+	+	+	-	-	-	-
Braiman et al. (2018)	+	?	?	?	-	-	-
Charland-Verville et al. (2014)	+	?	?	?	-	-	-
Chatelle et al. (2018)	+	?	-	-	-	-	-
Claassen et al. (2019)	+	?	?	-	-	-	-
Curley et al. (2018)	+	?	?	?	-	-	-
Edlow et al. (2017)	+	+	-	-	-	-	-
Faugeras et al. (2012)(Faugeras et al., 2012)	+	?	-	-	-	-	-
Fernandez-Espejo et al. (2015)	+	+	?	?	-	-	-

Forgacs et al. (2014)	+	+	+	?	-	-	-
Forgacs et al. (2016)	+	?	?	?	-	-	-
Gibson et al. (2016)	+	?	?	+	-	-	-
Goldfine et al. (2011)(Goldfine et al., 2011)	+	?	?	?	-	-	-
Guger et al. (2018)	+	?	-	+	-	-	-
Habbal et al. (2014)	+	?	?	-	-	-	-
Hauger et al. (2015)	+	+	?	-	-	-	-
Hinterberger et al. (2005)	+	?	+	?	-	-	-
Höller et al. (2013)	+	?	?	?	-	-	-
Liang et al. (2014)	+	?	+	?	-	-	-
Lulé et al. (2013)(Lulé et al., 2013)	+	?	?	?	-	-	-
Monti et al. (2009)	+	?	?	?	-	-	-
Monti et al. (2013)	+	?	?	?	-	-	-
Naci et al. (2013)	+	?	-	?	-	-	-
Owen et al. (2006)(A M Owen et al., 2006)	+	?	?	?	-	-	-
Pan et al. (2014)	+	?	?	+	-	-	-
Risetti et al. (2013)	+	?	?	-	-	-	-
Rodriguez Moreno et al. (2010)	+	?	?	-	-	-	-
Vassilieva et al. (2019)	+	-	+	?	- ?	-	-
CORTICAL ACTIVITY RELATED TO AUDITORY/SPEECH PROCESSING							
Balconi et al. (2015)	+	+	+	?	-	-	-
Balconi et al. (2013)	+	?	+	?	-	-	-
Beukema et al. (2016)	+	?	?	+	-	-	-
Coleman et al. (2007)	+	?	+	?	-	-	-
Coleman et al. (2009)	+	-	?	?	-	-	-
Coleman et al. (2009)	+	?	?	?	-	-	-
Crivelli et al. (2019)	+	?	+	?	-	-	-
Erlbeck et al. (2017)	+	?	?	-	-	-	-
Fernández-Espejo et al. (2010)	+	+	+	?	-	-	-
Formisano et al. (2019)	+	?	-	?	-	-	-
Kempny et al. (2018)	+	?	+	-	-	-	-
Kotchoubey et al. (2005)	+	?	+	?	-	-	-
Kotchoubey et al. (2009)	+	?	+	?	-	-	-
Kotchoubey et al. (2014)	+	+	?	+	-	-	-
Laureys et al. (2004)	+	?	?	-	-	-	-
Lechinger et al. (2016)	+	?	?	?	-	-	-
Li et al. (2018)	+	+	?	?	-	-	-
Naci et al. (2018)	+	?	-	-	-	-	-
Nigri et al. (2017)	+	?	?	+	-	-	-

Owen et al. (2005)	+	?	+	?	-	-	-
Perrin et al. (2006)	+	?	?	-	-	-	-
Rohaut et al. (2015)	+	+	-	-	-	-	-
Schabus et al. (2011)	+	?	?	-	-	-	-
Schiff et al. (2005)	+	?	+	?	-	-	-
Schnakers et al. (2015)	+	+	?	-	-	-	-
Schoenle et al. (2004)	+	?	+	?	-	-	-
Sergent et al. (2017)	+	?	-	-	-	-	-
Staffen et al. (2006)	+	+	+	?	-	-	-
Steppacher et al. (2013)	+	?	+	+	-	-	-
Tomaiuolo et al. (2016)	+	?	-	?	-	-	-
Wu et al. (2011)	+	?	?	?	-	-	-

+: high concern, ?: unclear concern, -: low concern.

First, patient selection was regarded to be at high risk of bias if the study includes a single case or convenience sample of patients. Second, the risk of index test bias (i.e., related to the language assessment) was considered as "unclear" if the investigators performing the language-related analyses were not specified to be blind of patients' diagnosis of DoC. A high risk of bias was estimated as soon as non-blinding was reported. Third, the reference standard (i.e., behavioral assessment of DoC) led to high risk of bias when the resulting DoC diagnosis did not comply with established consensus-based diagnostic criteria for UWS and MCS (J T Giacino et al., 2002; Multi-Society Task Force on PVS, 1994) (such as assessed using the CRS-R). We also concluded to such high risk of bias when the behavioral assessor was not blinded to the results of language assessment. Fourth, the flow and timing presented a high risk of bias when the patient flow could have introduced bias (e.g., no appropriate interval between index test and reference standard or patients assessed by different reference standard). Finally, the applicability concerns referred to the representativeness of the studies as regards the review question (i.e., target population, relevance of language assessment techniques, adherence to diagnostic criteria for DoC).

Brain metabolism but not grey matter volume underlies the presence of language function in the minimally conscious state

Supplementary material

Supplementary table 1. Brain glucose metabolism results in detail.

Supplementary table 2. Individual FDG-PET reports.

Supplementary table 3. Grey matter volume results in detail.

Supplementary analysis 1. Brain glucose metabolism in 16 MCS- versus 20 MCS+ patients.

Supplementary analysis 2. Brain glucose metabolism and grey matter structure in 7 MCS- versus 7 MCS+ patients.

Supplementary analysis 3. Brain glucose metabolism in 16 MCS- versus 41 MCS+ patients with time post-injury as covariate.

Supplementary analysis 4. Brain glucose metabolism in 14 MCS- versus 29 MCS+ right-handed patients.

Supplementary Table 1. Brain glucose metabolism results in detail.

Set		Cluster			Peak					Coordinates		
p	***c***	***p*(FWE-corr)**	**equiv *k***	***p*(unc)**	***p*(FWE-corr)**	***p*(FDR-corr)**	***T***	**equiv *Z***	***p*(unc)**	***x***	***y***	***z***
MCS- < MCS+												
0.290869	4	0.000	12540	0.000	0.000	0.000	5.806	5.323	0.000	-54	-38	-8
					0.229	0.007	3.861	3.699	0.000	-46	-70	28
		0.125	1564	0.049	0.548	0.017	3.436	3.318	0.000	-44	26	36
					0.645	0.021	3.326	3.218	0.001	-36	22	46
					0.668	0.023	3.301	3.195	0.001	-52	20	18
		0.482	506	0.242	0.593	0.019	3.386	3.273	0.001	20	8	68
					0.722	0.026	3.236	3.135	0.001	24	24	54
		0.788	126	0.570	0.812	0.033	3.118	3.027	0.001	-18	10	68
Hypometabolism in MCS-												
0.963361	3	0.000	61692	0.000	0.000	0.000	9.262	7.701	0.000	-10	12	2
					0.000	0.000	8.603	7.298	0.000	-6	-14	10
					0.000	0.000	8.461	7.208	0.000	-10	-6	12
		0.987	167	0.643	0.958	0.019	2.805	2.737	0.003	54	-54	50
		0.996	44	0.834	0.968	0.021	2.762	2.697	0.003	0	-24	-50
Hypometabolism in MCS+												
0.054847	10	0.000	43157	0.000	0.000	0.000	14.437	65535	0.000	-2	-14	6
					0.000	0.000	12.340	65535	0.000	0	-26	34
					0.000	0.000	11.775	65535	0.000	-8	10	4

		0.955	211	0.560	0.251	0.002	3.823	3.665	0.000	2	-22	-48
		0.902	386	0.420	0.470	0.004	3.527	3.400	0.000	-48	-70	44
		0.988	50	0.801	0.829	0.012	3.092	3.003	0.001	14	-44	84
		0.981	91	0.718	0.858	0.013	3.045	2.960	0.002	-12	-74	62
		0.993	18	0.894	0.872	0.014	3.022	2.938	0.002	2	-50	-50
		0.974	128	0.660	0.948	0.022	2.842	2.772	0.003	56	-58	48
					0.980	0.031	2.693	2.632	0.004	42	-72	50
		0.982	83	0.733	0.960	0.025	2.797	2.730	0.003	38	32	-18
		0.989	41	0.823	0.987	0.036	2.630	2.574	0.005	-34	30	-18
		0.994	10	0.927	0.989	0.038	2.609	2.554	0.005	-12	-46	84
Connectivity of left angular gyrus: MCS- < MCS+												
0.214957	3	0.000	3466	0.000	0.002	0.003	5.630	5.125	0.000	-12	30	40
					0.373	0.020	3.827	3.646	0.000	-14	46	56
					0.568	0.031	3.602	3.448	0.000	-8	62	44
		0.131	465	0.088	0.016	0.003	4.936	4.578	0.000	14	18	46
		0.757	5	0.888	0.763	0.046	3.380	3.250	0.001	-18	-78	32

MCS-: minimally conscious state minus; MCS+: minimally conscious state plus; FWE: family-wise error, FDR: false discovery rate.

Appendix II

Supplementary Table 2. Individual FDG-PET reports.

Patient	Hypometabolic areas	Areas showing relatively preserved metabolism	SUV mean
1	Left internal and external frontoparietal network and right frontal cortex and default mode network	Occipital areas, left parietal cortex, part of temporal areas, thalami, brain stem and cerebellum	2,7337
2	Bilateral internal and external fronto-parietal network of consciousness	Cerebellum, brainstem and part of the occipital poles	2,3773
3	Left hemisphere and right frontal cortex	Brain step, cerebellum, right inferior temporal area and sensory-motor cortices, thalami	3,0617
4	Left hemisphere and right mesio-frontal cortex	Right hemisphere, brain stem and cerebellum	4,1266
5	Anterior cingulate cortex, external left fronto-temporal network and thalami	Precuneus, occipital cortex and external parietal network	6,5171
6	Bilateral frontal lobules, left frontoparietal cortex and left temporal lobule	Brain stem, cerebellum, sensory-motor areas, occipital cortex and right temporo-parietal junction	3,3222
7	Internal and external bilateral consciousness frontoparietal networks	Part of motor areas, basal nuclei, brain stem and cerebellum	2,8015
8	Internal and external left consciousness frontoparietal networks	Internal and external right consciousness frontoparietal networks	4,7475
9	Internal and external bilateral consciousness frontoparietal networks	Bilateral sensory-motor and visual cortex, cerebellum, brain stem and thalami	2,7852
10	Anterior/mesio-frontal cingulate cortex, thalami, bilateral inferior temporal and (pre) frontal cortex and left (posterior) temporal lobules	Occipital cortices, sensory-motor areas, bilateral posterior parietal cortex, cerebellum, brain stem and bilateral posterior cingulate (precuneus) cortex	Biaised
11	The nearly entire right hemisphere, bilateral thalami and cingulate cortex.	Left hemisphere	5,2280
12	Bilateral frontoparietal regions	Sensory-motor cortex, insula, precuneus, bilateral occipital cortex, brain stem and cerebellum	Biaised
13	Left hemisphere	Right hemisphere	4,2024

14	Right parietal, temporal and frontal areas, and left occipital, temporal and parietal areas and thalami	Cerebellum and brainstem, anterior cingulate gyrus, precuneus, left frontal areas, left temporal pole, and right occipital cortices	2,9850
15	Fronto-parietal associative cortices (right>left), anterior cingulate cortex/mesiofrontal, bilateral posterior cingulate cortex/precuneus and thalami	Cerebellum, brainstem, right temporal inferior cortex, and left temporoparietal frontal junction.	3,9909
16	Cingulate cortex, bilateral temporo-occipito-parietal and fronto-parietal cortices, precuneus, thalami	Brain stem, cerebellum and bilateral sensory-motor regions	3,6259
27	Bilateral anterior cingulate cortex, left posterior cingulate cortex and precuneus, left occipito-temporal and frontal cortices, left thalamus	Brain stem, cerebellum, left and right temporal cortices (right>left), insula and right fronto-parieto-temporal junction	3,5205
28	Bilateral frontal cortex	Bilateral occipital, sensorimotor, temporal cortex and cerebellum	5,7370
29	Cerebellum, thalami, anterior and posterior cingulate cortex	Middle and lateral prefrontal cortex, sensory-motor regions and left temporo-parietal junction	4,3342
30	Thalami, bilateral mesiofrontal cortex, anterior cingulate cortex and temporal areas (right>left)	Temporo-fronto-parietal junctions	4,5118
31	Both thalami, anterior cingulate cortex/mesiofrontal areas and the whole right hemisphere	Most of the left hemisphere including the visual, auditory, sensory-motor and language areas	4,9307
32	Anterior cingulate cortex, left fronto-temporo-parietal cortex and thalami	Cerebellum and right temporo-parietal junction	5,6530
33	Right hemisphere, left temporo-parietal junction and thalamus	Brain stem, cerebellum, left cingulate and temporal cortices, bilateral occipital cortex	3,0131
34	Anterior/mesio-frontal cingulate cortex, thalami, cerebellum (R>L), bilateral prefrontal cortex	Bilateral orbitofrontal and occipital cortices, left cerebellum, right sensory-motor areas, inferior temporal cortices (left>right)	3,9799
35	Anterior cingulate cortex, thalami, frontal cortex, left temporo-fronto-parietal areas and parieto-occipital junction	Brain stem, cerebellum, right temporo-occipito-parietal areas, precuneus, left sensory-motor area	6,2070
36	Frontal and prefrontal cortex bilaterally, anterior cingulate cortex/mesio-frontal areas, right temporo-parietal cortex, precuneus and thalami	Cerebellum, occipital cortex bilaterally and left temporal cortex	3,4416
37	Bilateral temporo-parietal cortex	Brain stem, cerebellum, mesio-frontal bilateral regions, Wernicke area	3,3931

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38	Thalami and anterior cingulate cortex, right temporo-occipital and temporo-frontal junctions	Cerebellum, sensory-motor areas, occipital cortex (left>right), left hemisphere except prefrontal and right temporo-parietal cortices	6,0718
39	Anterior cingulate cortex, occipital and mesio-temporal cortices, thalami, brain stem and cerebellum	Orbitofrontal cortices, fronto-parietal and temporo-parietal junctions, anterior and posterior cingulate cortices (precuneus)	6,4685
40	Mesio-frontal/anterior and posterior cingulate cortex, posterior cingulate cortex, thalami, occipital cortex and bilateral sensory-motor areas	Precuneus, cerebellum, brain stem, bilateral inferior temporal and posterior parietal cortices	6,3947
41	Thalami, precuneus, middle frontal cortex, part of temporo-occipital and temporo-parietal cortices	Sensory-motor areas	4,6522
42	Thalami bilaterally, anterior cingulate and posterior cingulate cortices, precuneus/mesio-frontal cortex, and superior temporal gyrus	Brainstem, cerebellum, prefrontal cortex, temporo-parietal areas and inferior temporal cortex	3,9109
43	Bilateral thalami, bilateral middle and lateral frontal regions and right temporal cortex	Left hemisphere, brain stem, cerebellum, bilateral occipital areas, sensory-motor areas, bilateral parietal cortex, left temporal area and posterior cingulate cortex (precuneus)	3,3634
44	Thalami, anterior/mesio-frontal and posterior cingulate cortex, bilateral parietal and prefrontal cortices	Cerebellum, bilateral sensory-motor areas, occipital cortex, left inferior temporal cortex	3,9995
45	Anterior cingulate cortex, thalami, cerebellum, and fronto-parieto-temporal junctions	Occipital lobules, precuneus, and occipito-parietal junctions	5,1408
46	Posterior cingulate cortex, thalami, parieto-occipital regions, temporo-parietal junctions	Cerebellum, brain stem, anterior cingulate cortex, bilateral temporal and fronto-temporal cortices	4,6817
47	Thalami, posterior cingulate cortex, cerebellum, occipital, parietal and fronto-parietal areas	Brain stem, temporal poles and orbito-frontal and mesio-frontal cortices	3,3937

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48	Bilateral temporo-parietal and occipital cortex, posterior cingulate cortex (precuneus) and anterior/mesio-frontal cingulate cortex, cerebellum and thalami	Frontal cortex, temporal poles and brain stem	3,9370
49	Anterior/mesio-frontal and posterior/precuneus cingulate cortices, bilateral inferior temporal cortex, thalami and cerebellum	Prefrontal and occipital cortices bilaterally	6,5629
50	Thalami, bilateral anterior and posterior cingulate cortex and lateral frontal cortex, right occipital pole	Bilateral temporo-parieto-occipital areas, temporal poles, left sensory-motor area	4,8358
51	Mesio-frontal cortex, cerebellum and thalami	Fronto-temporo-parietal cortex bilaterally	5,0834
52	Right frontal, parietal areas, brainstem, and cerebellum	Left frontal, occipital and parietal cortex, bilateral temporal and bilateral orbitofrontal areas	6,4021
53	Right hemisphere (except sensory-motor areas) and left occipital cortex, thalami, anterior/mesio-frontal and posterior/precuneus cortices and left prefrontal cortex	Brain stem, cerebellum, right parieto-temporal frontal junction, left temporal and parietal cortices, left fronto-temporal junction	3,1056
54	Bilateral frontal regions, anterior/mesio-frontal cingulate cortex and posterior cingulate cortex (precuneus), thalami	Brain stem, cerebellum, occipital and sensory-motor cortices	5,0130
55	Anterior/mesio-frontal cingulate cortex, left inferior temporal and prefrontal cortices	Sensory-motor areas, bilateral occipital and posterior parietal cortices, right frontal and prefrontal cortices, posterior cingulate cortex (precuneus) and left cerebellum	3,8224
56	Thalami, mesio-frontal cortex and left temporo-parieto-occipital area	Part of the cerebellum, left sensory-motor area, right anterior cingulate cortex and almost all the right hemisphere	3,7990
57	Anterior/mesio-frontal cingulate cortex, posterior cingulate cortex (precuneus), bilateral fronto-parietal and right temporal cortices	Brain stem, cerebellum, thalami, bilateral sensory-motor areas, left temporal and occipital cortices	3,7095

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58	Thalami and bilateral inferior temporo-parietal cortex	Occipital cortex, anterior/mesio-frontal cingulate cortex, sensory-motor cortex	3,3332
59	Thalami, bilateral mesiofrontal areas and left lateral frontotemporal network and Broca and Wernicke areas	Posterior cingulate cortex/precuneus, right fronto-temporal-parietal areas and cerebellum	4,3791
60	Right hemisphere	Left hemisphere	4,9692
61	Posterior cingulate cortex, thalami, occipito-parieto-frontal regions and right superior temporal gyrus	Brain stem, cerebellum, orbito-frontal cortex, anterior cingulate cortex, part of occipital cortex, temporal cortex and left fronto-parieto-temporal junction	3,5633
62	Anterior and posterior cingulate cortex, fronto-lateral cortices, thalami, occipito-parietal cortices	Brainstem, cerebellum, mesio-frontal cortex, sensory-motor cortices	5,5263
63	Thalami, anterior cingulate/mesio-frontal cortex, bilateral frontal cortex	Posterior cingulate cortex (precuneus), bilateral inferior temporal and parietal cortices	3,6649
64	Cerebellum, anterior cingulate cortex, thalami, left fronto-parietal junction	Mesio-frontal cortex, precuneus, bilateral fronto-temporal-parietal (external consciousness) networks	4,7765
65	Left hemisphere, bilateral anterior cingulate cortex and mesio-frontal areas, bilateral thalami	Right hemisphere, cerebellum and occipital bilaterally	5,1104
66	Bilateral thalamus, prefrontal and posterior parietal associative cortices of both hemispheres and midline structures	Cerebellum, sensory-motor, orbitofrontal and mesiotemporal areas	3,5934
67	Left internal and external consciousness network and right thalamus	Right internal and external consciousness network, cerebellum, brain stem	5,2015

All results are thresholded at $p < 0.05$ uncorrected. SUV = Standard Uptake Value.

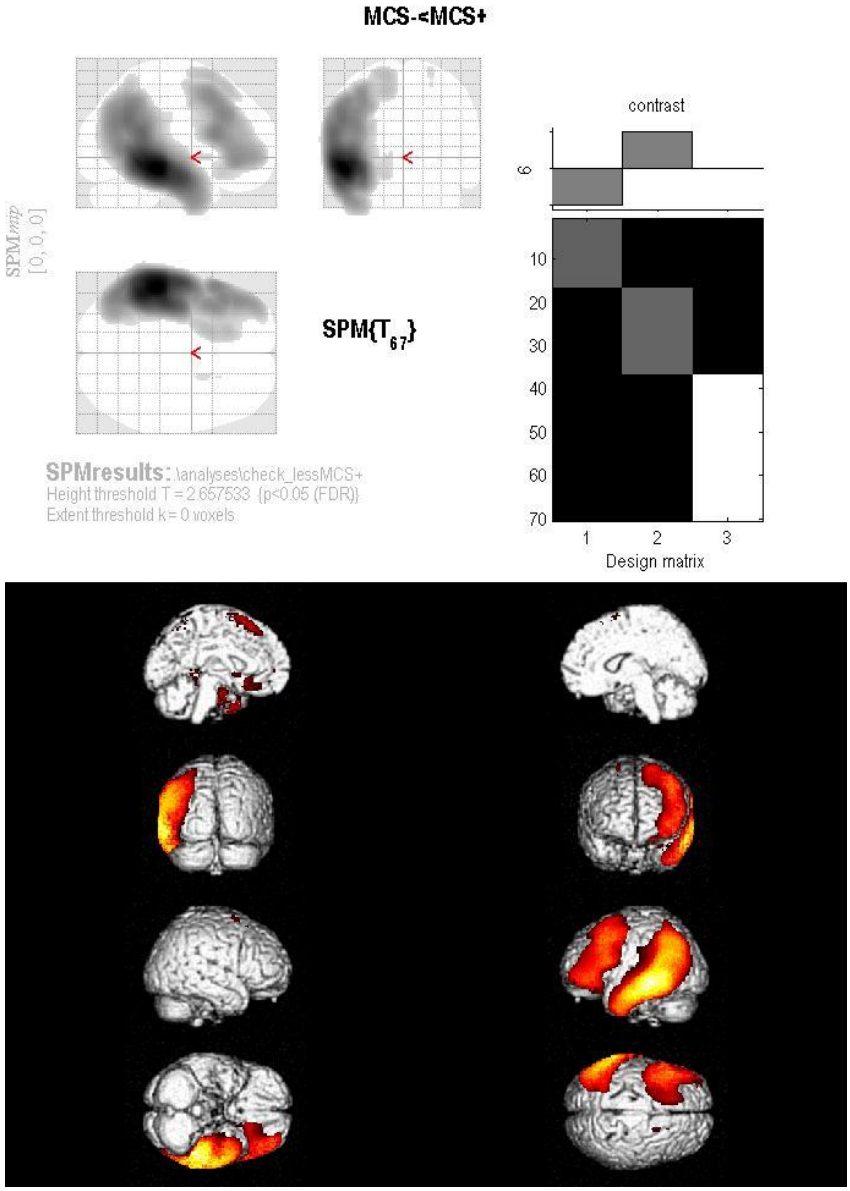
Appendix II

Supplementary Table 3. Grey matter volume results in detail.

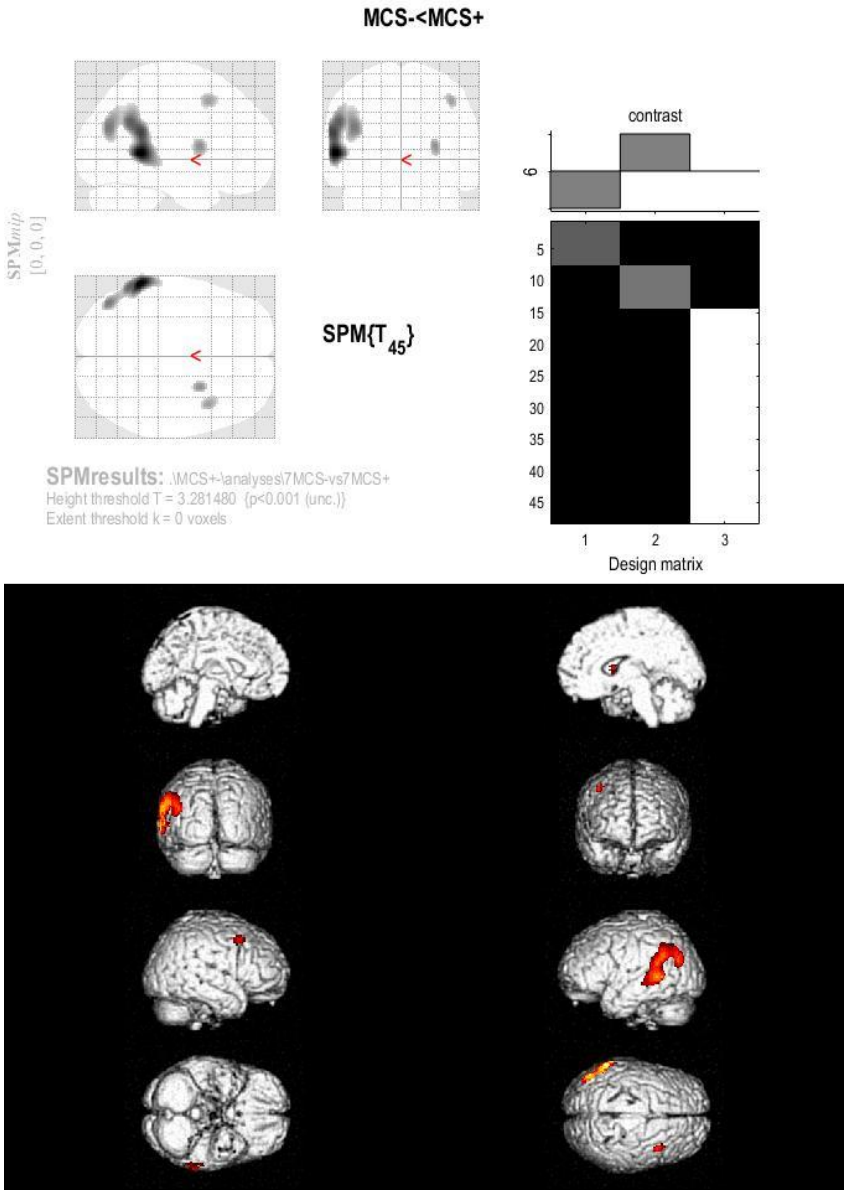
Set		Cluster				Peak					Coordinates		
p	***c***	***p*(FWE-corr)**	***p*(FDR-corr)**	**equiv *k***	***p*(unc)**	***p*(FWE-corr)**	***p*(FDR-corr)**	***T***	**equiv *Z***	***p*(unc)**	***x***	***y***	***z***
Hypotrophy in MCS-													
0.989115	5	0.000		112527	0.000	0.000	0.000	11.420	65535	0.000	6	-18	4
						0.000	0.000	10.634	65535	0.000	-9	-12	4
						0.000	0.000	10.632	65535	0.000	-12	11	-9
		1.000		1	0.995	0.000	0.000	7.436	6.605	0.000	18	21	-14
		1.000		59	0.923	0.000	0.000	5.539	5.154	0.000	-35	-17	9
		1.000		1	0.995	0.010	0.000	4.660	4.418	0.000	-45	-12	9
		1.000		150	0.861	0.884	0.006	2.794	2.734	0.003	-32	-42	53
						0.998	0.021	2.245	2.214	0.013	-29	-35	60
Hypotrophy in MCS+													
0.917994	8	0.000		125146	0.000	0.000	0.000	14.861	65535	0.000	6	-18	4
						0.000	0.000	13.585	65535	0.000	-12	9	-9
						0.000	0.000	13.505	65535	0.000	-9	-14	4
		1.000		1	0.995	0.000	0.000	8.147	7.102	0.000	18	21	-14
		1.000		59	0.928	0.000	0.000	5.876	5.425	0.000	-35	-17	9
		1.000		1	0.995	0.001	0.000	5.391	5.033	0.000	-45	-12	9
		1.000		427	0.756	0.222	0.000	3.649	3.524	0.000	-29	-35	60
		1.000		130	0.881	0.622	0.002	3.138	3.056	0.001	-63	-45	17
		1.000		3	0.990	1.000	0.033	1.945	1.927	0.027	-38	-74	-15
		1.000		2	0.992	1.000	0.047	1.778	1.768	0.039	-45	-57	18

MCS-: minimally conscious state minus; MCS+: minimally conscious state plus; FWE: family-wise error, FDR: false discovery rate.

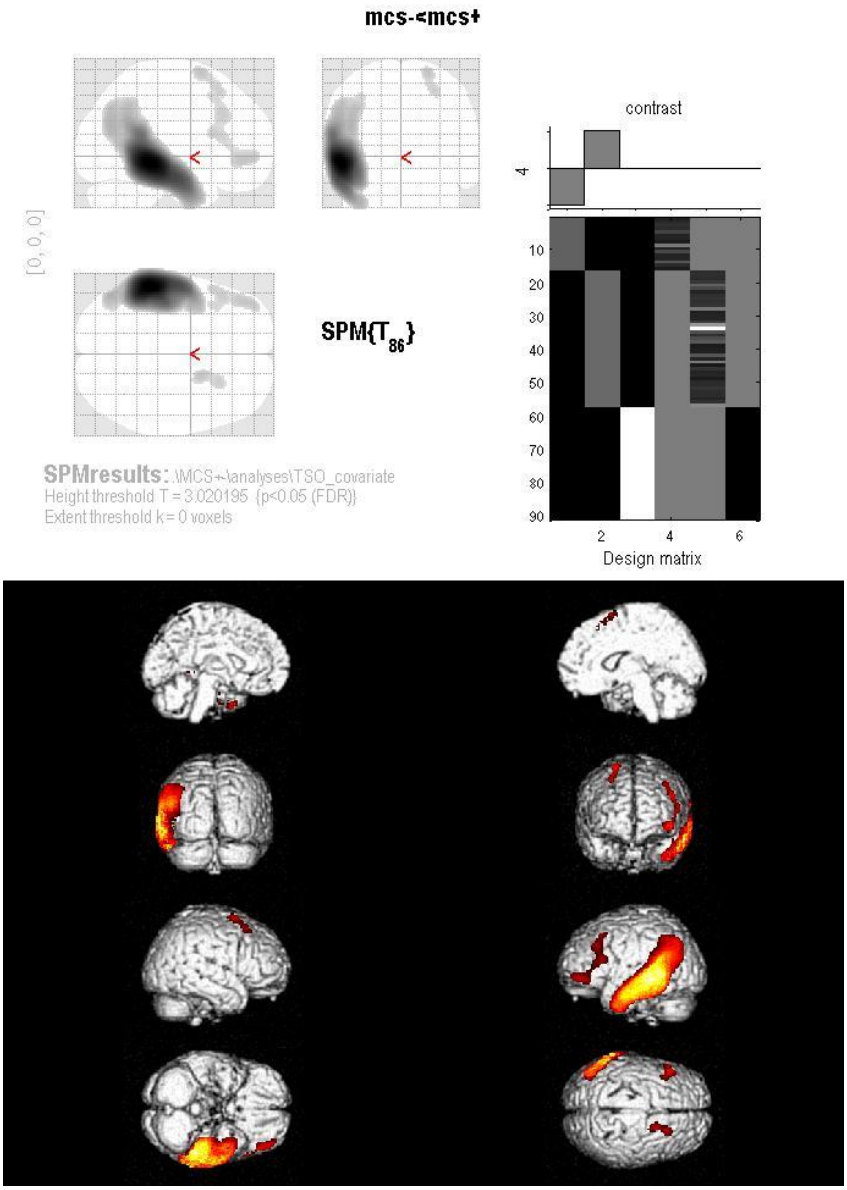
Supplementary Analysis 1. Brain glucose metabolism in 16 MCS- versus 20 MCS+ patients.



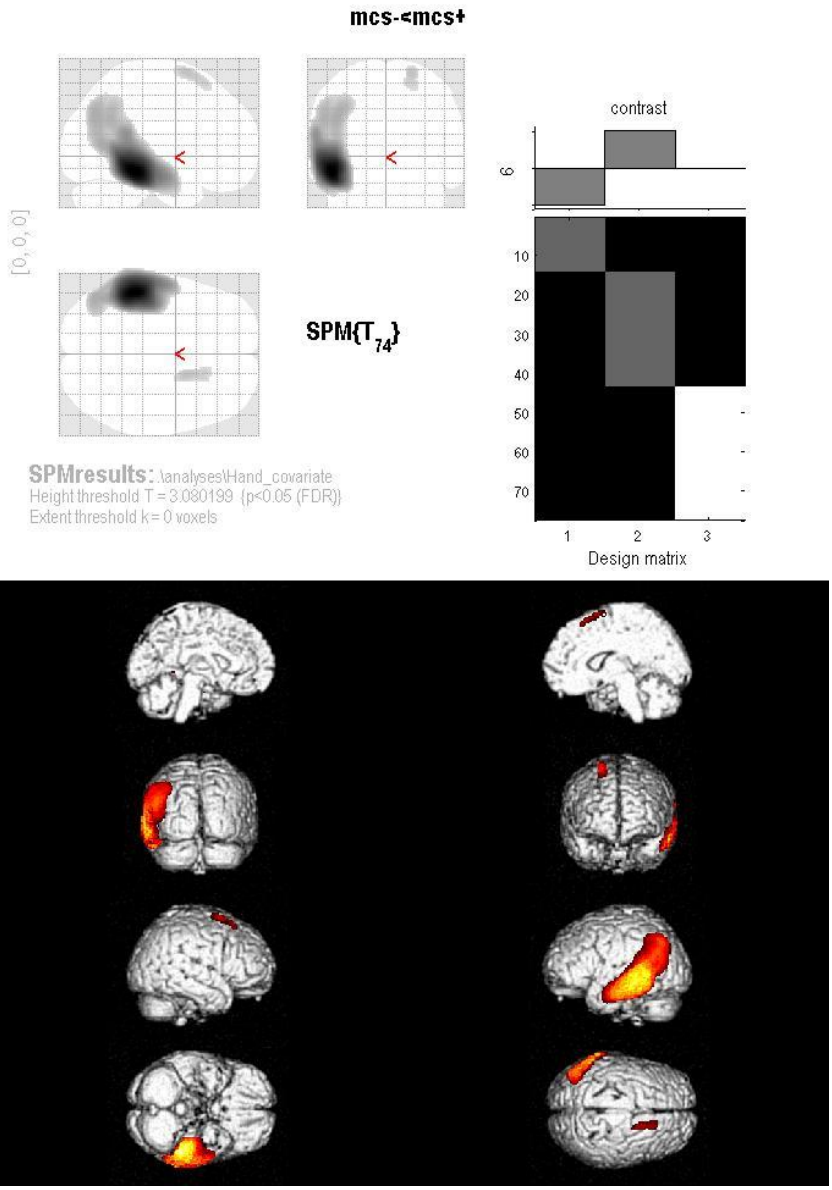
Supplementary Analysis 2. Brain glucose metabolism in 7 MCS- versus 7 MCS+ patients.



Supplementary Analysis 3. Brain glucose metabolism in 16 MCS- versus 41 MCS+ patients with time post-injury as covariate.



Supplementary Analysis 4. Brain glucose metabolism in 14 MCS- versus 29 MCS+ right-handed patients.



APPENDIX III

Clinical sub-categorization of minimally conscious state according to resting functional connectivity

Supplementary Material

Supplementary material 1. Tables S1 and S2 - Statistical values

Supplementary material 2. Comparison between healthy control subjects and patients

- Resting functional connectivity analysis
- Effect-sizes and confidence interval for all investigated seeds
- Voxel-based morphometry analysis

Supplementary marterial 3. Thalamocortical connectivity**.**

Supplementary marterial 4: Table S3 - Interhemispheric connectivity analysis in patients as compared to healthy control subjects

Supplementary marterial 5: Default mode network anticorrelations

Supplementary Material 1

Table S1. Statistical values of the clusters functionally connected with the four networks in each subject group.

Seed	Group	Set		Cluster			Peak					Coordinates		
		p	c	*p*(FWE-corr)	equiv k	*p*(unc)	*p*(FWE-corr)	*p*(FDR-corr)	T	equiv Z	*p*(unc)	x,y,z {mm}		
Left DLPFC	MCS-	0,0000	6	0,0000	4045	0,0000	0,0018	0,0003	22,9328	5,675	0,0000	-42	26	36
				0,0000	539	0,0000	0,5155	0,0015	11,0825	4,6155	0,0000	48	38	2
				0,0000	505	0,0000	0,7603	0,0022	9,9609	4,4462	0,0000	-30	44	0
				0,0044	177	0,0001	0,9778	0,0059	7,968	4,0805	0,0000	-20	6	60
				0,0008	229	0,0000	0,9998	0,0128	6,5256	3,7413	0,0001	-48	-60	54
				0,0212	132	0,0007	1,0000	0,0157	6,1545	3,64	0,0001	42	30	32
	MCS+	0,0000	4	0,0000	8508	0,0000	0,0031	0,0003	17,9334	5,5825	0,0000	-42	24	32
				0,0000	538	0,0000	0,4559	0,0015	9,9244	4,6214	0,0000	-32	-76	54
				0,0000	641	0,0000	0,5896	0,0020	9,2393	4,4972	0,0000	-48	-40	-6
				0,0000	386	0,0000	0,9877	0,0064	6,7207	3,9257	0,0000	-42	-36	42
	HCS	0,0000	9	0,0000	18267	0,0000	0,0000	0,0000	43,9444	65535	0,0000	-44	20	32
				0,0000	6353	0,0000	0,0000	0,0000	16,2101	65535	0,0000	-42	-48	48
				0,0000	7685	0,0000	0,0000	0,0000	13,9796	65535	0,0000	52	26	30
				0,0000	6508	0,0000	0,0000	0,0000	11,2829	7,2291	0,0000	30	-66	-30
				0,0000	3047	0,0000	0,0000	0,0000	9,8036	6,7109	0,0000	-62	-46	-6
				0,0000	2916	0,0000	0,0000	0,0000	9,3955	6,5536	0,0000	34	-58	44
				0,0049	299	0,0003	0,0003	0,0000	7,9135	5,9193	0,0000	-6	-30	38
				0,0127	248	0,0007	0,0033	0,0000	6,9946	5,4684	0,0000	-6	-24	-24

				0,0304	204	0,0018	0,3221	0,0001	5,0792	4,3508	0,0000	-32	-64	-34
Left IPL	MCS-	0,0000	6	0,0000	4394	0,0000	0,0007	0,0001	25,7265	5,8286	0,0000	-44	-42	44
				0,0000	545	0,0000	0,9336	0,0029	8,5674	4,2010	0,0000	-44	6	30
				0,0378	119	0,0012	0,9585	0,0035	8,2567	4,1398	0,0000	-56	-58	-10
				0,0472	113	0,0016	0,9593	0,0035	8,2457	4,1376	0,0000	-8	30	-12
				0,0000	370	0,0000	0,9989	0,0080	6,8815	3,8324	0,0001	-2	-40	50
				0,0455	114	0,0015	1,0000	0,0196	5,6642	3,4953	0,0002	-62	-22	-16
	MCS+	0,0000	6	0,0000	5743	0,0000	0,0003	0,0001	23,2329	5,9672	0,0000	-42	-48	44
				0,0000	1176	0,0000	0,2365	0,0004	10,8559	4,7748	0,0000	-50	36	18
				0,0103	180	0,0004	0,2452	0,0004	10,8093	4,7675	0,0000	-48	12	56
				0,0000	1185	0,0000	0,4500	0,0006	9,8610	4,6104	0,0000	4	-36	44
				0,0160	165	0,0006	0,7922	0,0013	8,1993	4,2862	0,0000	28	-70	44
				0,0015	251	0,0001	0,8744	0,0017	7,7605	4,1876	0,0000	-14	56	44
	HCS	0,0000	9	0,0000	16599	0,0000	0,0000	0,0000	49,6801	65535	0,0000	-44	-46	48
				0,0000	14566	0,0000	0,0000	0,0000	16,4874	65535	0,0000	-44	50	6
				0,0000	10254	0,0000	0,0000	0,0000	15,4966	65535	0,0000	46	24	36
				0,0000	1453	0,0000	0,0000	0,0000	12,8426	65535	0,0000	0	-30	38
				0,0000	4572	0,0000	0,0000	0,0000	12,2559	7,6965	0,0000	58	-48	-6
				0,0000	2666	0,0000	0,0000	0,0000	11,0384	7,2987	0,0000	-54	-58	-10
				0,0000	985	0,0000	0,0001	0,0000	8,1744	6,1405	0,0000	-12	-78	-28
				0,0199	233	0,0012	0,0002	0,0000	7,8859	6,0030	0,0000	34	20	-4
				0,0051	308	0,0003	0,0081	0,0000	6,4760	5,2616	0,0000	-6	-22	-24
Right DLPFC	MCS-	0,0000	5	0,0000	2944	0,0000	0,0038	0,0009	20,9132	5,5493	0,0000	46	18	32

				0,0038	186	0,0001	0,7977	0,0058	9,6554	4,3961	0,0000	4	-42	44
				0,0042	183	0,0001	0,9206	0,0078	8,7018	4,2266	0,0000	60	-40	48
				0,0006	246	0,0000	0,9874	0,0125	7,6618	4,0147	0,0000	-48	6	30
				0,0011	226	0,0000	0,9890	0,0127	7,6057	4,0024	0,0000	46	-54	50
	MCS+	0,0000	3	0,0000	3977	0,0000	0,0009	0,0003	20,6067	5,7915	0,0000	48	24	38
				0,0000	1979	0,0000	0,9196	0,0066	7,4035	4,1024	0,0000	48	-42	54
				0,0106	185	0,0004	0,9861	0,0098	6,6326	3,9014	0,0000	10	48	44
	HCS	0,0000	9	0,0000	16619	0,0000	0,0000	0,0000	45,1626	65535	0,0000	46	24	32
				0,0000	11671	0,0000	0,0000	0,0000	17,2623	65535	0,0000	46	-46	54
				0,0000	7936	0,0000	0,0000	0,0000	15,1006	65535	0,0000	-48	24	32
				0,0000	4804	0,0000	0,0000	0,0000	13,8844	65535	0,0000	-42	-48	44
				0,0000	2863	0,0000	0,0000	0,0000	11,9364	7,435	0,0000	-8	-82	-24
				0,0000	1832	0,0000	0,0002	0,0000	8,053	5,9836	0,0000	-60	-40	-16
				0,0389	189	0,0023	0,0277	0,0000	6,1501	5,0079	0,0000	10	-12	12
				0,0149	236	0,0009	0,2611	0,0000	5,1906	4,4233	0,0000	6	-22	-24
				0,0132	242	0,0008	0,4941	0,0001	4,8531	4,2007	0,0000	12	-78	-24
Right IPL	MCS-	0,0000	7	0,0000	3536	0,0000	0,0062	0,0011	19,6140	5,4605	0,0000	48	-54	50
				0,0000	943	0,0000	0,2962	0,0018	11,9223	4,7293	0,0000	40	2	42
				0,0002	282	0,0000	0,3852	0,0019	11,5171	4,6757	0,0000	-54	-64	-16
				0,0047	178	0,0002	0,4613	0,0020	11,2467	4,6386	0,0000	46	54	6
				0,0498	111	0,0016	0,7979	0,0031	9,6691	4,3984	0,0000	6	-34	50
				0,0429	115	0,0014	0,9330	0,0047	8,5867	4,2047	0,0000	28	66	24
				0,0062	170	0,0002	0,9915	0,0073	7,5158	3,9823	0,0000	40	38	30

	MCS+	0,0000	6	0,0000	4136	0,0000	0,0035	0,0004	17,6901	5,5616	0,0000	42	-42	50
				0,0000	1082	0,0000	0,1716	0,0013	11,2764	4,8389	0,0000	10	-40	48
				0,0000	621	0,0000	0,9307	0,0075	7,3475	4,0886	0,0000	46	50	30
				0,0313	145	0,0012	0,9956	0,0127	6,3263	3,8142	0,0001	-62	-22	36
				0,0261	151	0,0010	0,9997	0,0174	5,7824	3,6471	0,0001	22	48	44
				0,0412	136	0,0016	1,0000	0,0211	5,4229	3,5271	0,0002	30	62	8
	HCS	0,0000	8	0,0000	17025	0,0000	0,0000	0,0000	43,4746	65535	0,0000	48	-48	48
				0,0000	17071	0,0000	0,0000	0,0000	17,7173	65535	0,0000	42	54	0
				0,0000	2464	0,0000	0,0000	0,0000	12,6174	7,7995	0,0000	66	-40	-6
				0,0000	6171	0,0000	0,0000	0,0000	9,7169	6,8068	0,0000	-48	50	6
				0,0000	2902	0,0000	0,0000	0,0000	9,3390	6,6536	0,0000	-14	-82	-28
				0,0019	362	0,0001	0,0002	0,0000	7,9939	6,0550	0,0000	10	-12	12
				0,0000	1948	0,0000	0,0003	0,0000	7,6821	5,9031	0,0000	-62	-46	-4
				0,0064	291	0,0004	0,0054	0,0000	6,6364	5,3522	0,0000	10	-22	-30
Left STG	MCS-	0,0000	3	0,0000	4811	0,0000	0,0004	0,0000	27,663	5,9238	0,0000	-44	-4	8
				0,0009	238	0,0000	0,8659	0,0023	9,1262	4,3046	0,0000	52	-30	20
				0,0276	130	0,0009	0,9909	0,0049	7,4897	3,9764	0,0000	34	14	14
	MCS+	0,0000	5	0,0000	8075	0,0000	0,0018	0,0003	19,132	5,6806	0,0000	-48	-6	8
				0,0000	2854	0,0000	0,0880	0,0004	12,1989	4,9701	0,0000	46	-12	20
				0,0306	127	0,0010	0,9657	0,0028	7,251	4,0646	0,0000	-18	-30	72
				0,0248	133	0,0008	0,9873	0,0034	6,8719	3,9665	0,0000	-18	-6	-48
				0,0169	144	0,0006	0,9973	0,0044	6,4376	3,8464	0,0001	60	30	6
	HCS	0,0000	3	0,0000	40216	0,0000	0,0000	0,0000	39,0114	65535	0,0000	-44	-6	8

				0,0086	263	0,0005	0,0613	0,0000	5,8277	4,8192	0,0000	-24	-60	-22
				0,0049	293	0,0003	0,3477	0,0001	5,0508	4,3322	0,0000	16	-60	-16
Right STG	MCS-	0,0000	3	0,0000	5210	0,0000	0,0008	0,0002	25,3952	5,8115	0,0000	40	2	6
				0,0230	136	0,0008	0,0333	0,0004	15,8354	5,1555	0,0000	-42	-82	20
				0,0000	698	0,0000	0,6445	0,0014	10,5609	4,5395	0,0000	-44	-16	6
	MCS+	0,0000	2	0,0000	5474	0,0000	0,0006	0,0001	21,6894	5,8671	0,0000	52	-6	8
				0,0000	1008	0,0000	0,0466	0,0004	13,1396	5,092	0,0000	-42	-12	6
	HCS	0,0000	6	0,0000	37351	0,0000	0,0000	0,0000	41,5588	65535	0,0000	42	-4	12
				0,0061	279	0,0003	0,0096	0,0000	6,5812	5,2489	0,0000	0	24	2
				0,0001	564	0,0000	0,0348	0,0000	6,0633	4,9578	0,0000	52	-60	-4
				0,0000	574	0,0000	0,0482	0,0000	5,9305	4,8802	0,0000	-56	-64	6
				0,0049	291	0,0003	0,1343	0,0000	5,4993	4,619	0,0000	-18	-60	-18
				0,0047	293	0,0003	0,1483	0,0000	5,4559	4,5919	0,0000	12	-58	-24
MPFC	MCS-	0,0000	3	0,0000	5057	0,0000	0,0141	0,0018	17,6763	5,3139	0,0000	4	54	30
				0,0003	271	0,0000	0,9964	0,0094	7,207	3,9112	0,0000	-32	38	24
				0,0058	173	0,0002	0,9993	0,0116	6,7616	3,8023	0,0001	-2	26	60
	MCS+	0,0000	2	0,0000	11386	0,0000	0,0001	0,0000	26,2404	6,1413	0,0000	4	56	24
				0,0040	211	0,0002	0,9064	0,0015	7,5789	4,1449	0,0000	48	0	44
	HCS	0,0000	14	0,0000	15036	0,0000	0,0000	0,0000	36,9309	65535	0,0000	-2	54	26
				0,0000	2699	0,0000	0,0000	0,0000	11,1104	7,1725	0,0000	6	-52	26
				0,0000	2426	0,0000	0,0000	0,0000	9,9292	6,758	0,0000	-44	-60	24
				0,0000	1320	0,0000	0,0000	0,0000	9,6934	6,6691	0,0000	28	-82	-30
				0,0000	3456	0,0000	0,0000	0,0000	9,6231	6,6422	0,0000	58	6	-24

				0,0000	5263	0,0000	0,0000	0,0000	9,2856	6,51	0,0000	-60	0	-18
				0,0000	1605	0,0000	0,0001	0,0000	8,5702	6,2133	0,0000	54	-54	24
				0,0022	362	0,0001	0,0013	0,0000	7,3391	5,6432	0,0000	-14	-104	18
				0,0000	882	0,0000	0,0045	0,0000	6,8499	5,3928	0,0000	-24	-78	-36
				0,0011	408	0,0001	0,0119	0,0000	6,4586	5,1816	0,0000	6	-54	-40
				0,0004	475	0,0000	0,0183	0,0000	6,2865	5,0855	0,0000	-24	-18	-12
				0,0031	341	0,0002	0,0537	0,0000	5,8491	4,8319	0,0000	28	-16	-16
				0,0001	613	0,0000	0,0996	0,0000	5,5906	4,6755	0,0000	34	-96	18
				0,0007	438	0,0000	0,1452	0,0000	5,4277	4,5743	0,0000	-38	14	48
PCC	MCS-	0,0000	4	0,0000	8258	0,0000	0,0091	0,0003	18,6838	5,3924	0,0000	0	-64	26
				0,0454	117	0,0015	0,7509	0,0015	9,8899	4,4347	0,0000	-30	56	36
				0,0096	162	0,0003	0,8758	0,0020	9,0303	4,2874	0,0000	-42	48	18
				0,0000	357	0,0000	0,9859	0,0035	7,6528	4,0128	0,0000	50	-80	30
	MCS+	0,0000	3	0,0000	8876	0,0000	0,0001	0,0000	27,6804	6,2164	0,0000	4	-52	26
				0,0002	320	0,0000	0,3696	0,0004	10,2932	4,6841	0,0000	6	60	0
				0,0283	140	0,0010	0,6252	0,0008	9,0707	4,465	0,0000	24	66	12
	HCS	0,0000	11	0,0000	9526	0,0000	0,0000	0,0000	56,0471	65535	0,0000	0	-54	30
				0,0000	3792	0,0000	0,0000	0,0000	17,2812	65535	0,0000	-44	-66	32
				0,0000	15193	0,0000	0,0000	0,0000	16,4024	65535	0,0000	-2	48	-6
				0,0000	3269	0,0000	0,0000	0,0000	15,265	65535	0,0000	52	-54	26
				0,0000	3519	0,0000	0,0000	0,0000	13,947	65535	0,0000	-56	-4	-22
				0,0000	3937	0,0000	0,0000	0,0000	13,6217	65535	0,0000	58	-6	-18
				0,0000	1231	0,0000	0,0000	0,0000	10,657	7,0192	0,0000	24	-18	-22
				0,0000	848	0,0000	0,0003	0,0000	8,0197	5,9684	0,0000	10	-54	-40

0,0000	596	0,0000	0,0043	0,0000	6,8867	5,4122	0,0000	28	-84	-30
0,0015	369	0,0001	0,0070	0,0000	6,6921	5,3089	0,0000	-2	-16	6
0,0000	715	0,0000	0,0319	0,0000	6,0839	4,9698	0,0000	-26	-78	-34

MCS = minimally conscious state; HCS = healthy control subjects; DLPFC = dorso-lateral prefrontal cortex; IPL = inferior parietal lobule; STG = superior temporal gyrus; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex.

Appendix III

Table S2. Statistical values of the clusters obtained by the between-group comparisons.

Seed	Contrast	Set		Cluster			Peak					Coordinates		
		p	c	*p*(FWE-corr)	equiv k	*p*(unc)	*p*(FWE-corr)	*p*(FDR-corr)	T	equiv Z	*p*(unc)	x,y,z {mm}		
Left DLPFC	MCS+>MCS-	0,0031	1	0,0031	286	0,0002	0,3888	0,1438	6,1380	4,3977	0,0000	-44	-52	-22
	HCS>MCS+	0,0000	4	0,0001	555	0,0000	0,1168	0,0211	5,2892	4,6163	0,0000	46	48	-12
				0,0000	894	0,0000	0,1359	0,0211	5,2302	4,5756	0,0000	28	-66	-30
				0,0003	497	0,0000	0,2774	0,0211	4,9356	4,3687	0,0000	34	-58	44
				0,0000	629	0,0000	0,3836	0,0211	4,7858	4,2610	0,0000	52	32	20
	HCS>MCS-	0,0000	4	0,0000	1158	0,0000	0,0706	0,0173	5,5103	4,7530	0,0000	28	-66	-30
				0,0094	273	0,0006	0,1277	0,0173	5,2831	4,5999	0,0000	46	48	-16
				0,0398	197	0,0025	0,1479	0,0173	5,2248	4,5600	0,0000	-44	54	0
				0,0001	533	0,0000	0,3554	0,0173	4,8472	4,2952	0,0000	-30	-64	48
Left IPL	HCS>MCS+	0,0000	2	0,0000	1580	0,0000	0,0002	0,0000	7,4596	5,9431	0,0000	46	-48	50
				0,0000	3054	0,0000	0,0381	0,0003	5,7036	4,8946	0,0000	46	50	0
	HCS>MCS-	0,0000	6	0,0000	1395	0,0000	0,0000	0,0000	8,8717	6,6227	0,0000	48	-46	56
				0,0000	2349	0,0000	0,0002	0,0000	7,6627	6,0276	0,0000	40	48	-10
				0,0270	219	0,0017	0,0207	0,0002	5,9546	5,0416	0,0000	58	-48	-6
				0,0001	541	0,0000	0,1297	0,0009	5,2720	4,5923	0,0000	-44	50	0
				0,0039	327	0,0002	0,2192	0,0014	5,0585	4,4447	0,0000	46	-72	-30
				0,0310	212	0,0019	0,3678	0,0022	4,8257	4,2797	0,0000	12	-78	-30
Right DLPFC	HCS>MCS+	0,0000	1	0,0000	1266	0,0000	0,0013	0,0003	6,8767	5,6171	0,0000	-32	-58	38
	HCS>MCS-	0,0000	1	0,0000	1678	0,0000	0,0013	0,0002	6,9260	5,6250	0,0000	-32	-58	38

Right IPL	HCS>MCS+	0,0000	3	0,0000	1547	0,0000	0,0002	0,0000	7,5752	6,0053	0,0000	-42	-54	54
				0,0000	689	0,0000	0,0287	0,0003	5,8058	4,9613	0,0000	46	54	0
				0,0119	266	0,0007	0,8940	0,0127	4,1808	3,8082	0,0001	-38	48	0
	HCS>MCS-	0,0000	4	0,0000	1261	0,0000	0,0111	0,0018	6,1824	5,1841	0,0000	-44	-48	48
				0,0001	551	0,0000	0,0539	0,0021	5,6115	4,8200	0,0000	36	54	2
				0,0100	269	0,0006	0,6790	0,0108	4,4788	4,0262	0,0000	34	14	44
				0,0474	188	0,0029	0,8039	0,0141	4,3343	3,9178	0,0000	4	32	38
Left STG	HCS>MCS+	0,0000	3	0,0000	3934	0,0000	0,0006	0,0001	7,1525	5,7739	0,0000	60	-24	32
				0,0000	1185	0,0000	0,0110	0,0002	6,1666	5,1909	0,0000	4	0	54
				0,0615	171	0,0037	0,1791	0,0010	5,1412	4,5138	0,0000	-60	-30	32
	HCS>MCS-	0,0000	6	0,0000	5755	0,0000	0,0000	0,0000	8,1087	6,2561	0,0000	60	-24	26
				0,0000	733	0,0000	0,0188	0,0002	5,9976	5,0688	0,0000	10	6	44
				0,0431	191	0,0026	0,6024	0,0027	4,5658	4,0907	0,0000	12	-78	26
				0,0562	178	0,0035	0,6046	0,0027	4,5634	4,0889	0,0000	-48	-84	6
				0,0030	334	0,0002	0,7377	0,0037	4,4182	3,9809	0,0000	-14	-66	-16
				0,1010	150	0,0064	0,9554	0,0076	4,0712	3,7162	0,0001	-24	-48	68
Right STG	HCS>MCS+	0,0000	4	0,0000	3513	0,0000	0,0087	0,0020	6,2509	5,2433	0,0000	-54	-22	14
				0,0000	975	0,0000	0,0572	0,0026	5,5800	4,8129	0,0000	-8	0	50
				0,0050	298	0,0003	0,1877	0,0029	5,1246	4,5023	0,0000	-18	-40	62
				0,0138	244	0,0008	0,1891	0,0029	5,1216	4,5001	0,0000	-26	-12	-22
	HCS>MCS-	0,0000	5	0,0000	4224	0,0000	0,0011	0,0004	7,0049	5,6697	0,0000	-54	0	6
				0,0002	517	0,0000	0,5345	0,0040	4,6382	4,1439	0,0000	24	-4	48
				0,0003	485	0,0000	0,5943	0,0045	4,5735	4,0964	0,0000	-30	-40	50

				0,0039	319	0,0002	0,7502	0,0063	4,4029	3,9694	0,0000	58	-22	56
				0,0030	334	0,0002	0,8780	0,0085	4,2335	3,8412	0,0001	60	6	26
MPFC	HCS>MCS+	0,0000	8	0,0012	414	0,0001	0,0271	0,0093	5,8138	4,9665	0,0000	24	-10	-12
				0,0017	392	0,0001	0,0599	0,0093	5,5258	4,7767	0,0000	-30	-40	26
				0,0009	438	0,0001	0,0833	0,0093	5,4033	4,6942	0,0000	6	-52	26
				0,0271	228	0,0018	0,1095	0,0093	5,2996	4,6235	0,0000	-26	-12	-12
				0,0161	257	0,0011	0,3474	0,0121	4,8181	4,2844	0,0000	28	-78	-30
				0,0358	213	0,0024	0,5317	0,0155	4,5981	4,1236	0,0000	6	-52	-40
				0,1536	138	0,0108	0,6876	0,0192	4,4307	3,9987	0,0000	6	54	-10
				0,1282	147	0,0089	0,7311	0,0198	4,3825	3,9624	0,0000	-26	-76	-34
	HCS>MCS-	0,0000	4	0,0000	896	0,0000	0,0360	0,0058	5,7384	4,9030	0,0000	-38	-58	26
				0,0000	1812	0,0000	0,0379	0,0058	5,7193	4,8905	0,0000	-12	-30	24
				0,0003	521	0,0000	0,0622	0,0058	5,5368	4,7706	0,0000	58	2	-24
				0,0000	1049	0,0000	0,3189	0,0064	4,8764	4,3160	0,0000	-54	0	-22
PCC	HCS>MCS+	0,0000	10	0,0000	719	0,0000	0,0006	0,0001	7,1380	5,7658	0,0000	-6	-58	30
				0,0000	1018	0,0000	0,0017	0,0001	6,7934	5,5688	0,0000	-66	-16	-10
				0,0000	2134	0,0000	0,0065	0,0002	6,3326	5,2936	0,0000	0	48	-6
				0,0000	961	0,0000	0,0082	0,0002	6,2525	5,2443	0,0000	60	-6	-16
				0,0007	430	0,0000	0,0375	0,0005	5,7147	4,9019	0,0000	34	-12	-18
				0,0008	421	0,0001	0,0687	0,0007	5,4938	4,7553	0,0000	-26	-22	-12
				0,0010	408	0,0001	0,0867	0,0008	5,4069	4,6966	0,0000	22	30	48
				0,0030	341	0,0002	0,1300	0,0010	5,2519	4,5907	0,0000	16	-6	50
				0,0014	388	0,0001	0,2887	0,0018	4,9222	4,3592	0,0000	-8	-42	-42
				0,0275	218	0,0017	0,7542	0,0049	4,3766	3,9579	0,0000	-50	-70	30

HCS>MCS-	0,0000	9	0,0000	2462	0,0000	0,0042	0,0010	6,5143	5,3854	0,0000	-6	44	-6
			0,1483	135	0,0099	0,0129	0,0010	6,1219	5,1466	0,0000	10	-10	-4
			0,0008	424	0,0001	0,0151	0,0010	6,0654	5,1113	0,0000	-26	-22	-18
			0,0676	173	0,0043	0,0322	0,0013	5,7932	4,9384	0,0000	-60	0	-22
			0,0001	565	0,0000	0,0938	0,0017	5,3967	4,6770	0,0000	22	36	54
			0,1870	124	0,0128	0,1028	0,0017	5,3613	4,6530	0,0000	-2	-58	30
			0,0006	444	0,0000	0,1098	0,0018	5,3361	4,6359	0,0000	54	-10	-18
			0,1648	130	0,0111	0,8283	0,0085	4,2949	3,8880	0,0001	-18	32	42
			0,1614	131	0,0108	0,9571	0,0134	4,0534	3,7023	0,0001	-50	-70	30

MCS = minimally conscious state; HCS = healthy control subjects; DLPFC = dorso-lateral prefrontal cortex; IPL = inferior parietal lobule; STG = superior temporal gyrus; MPFC = medial prefrontal cortex; PCC = posterior cingulate cortex.

Supplementary Material 2

- Resting state fMRI inter-group comparisons

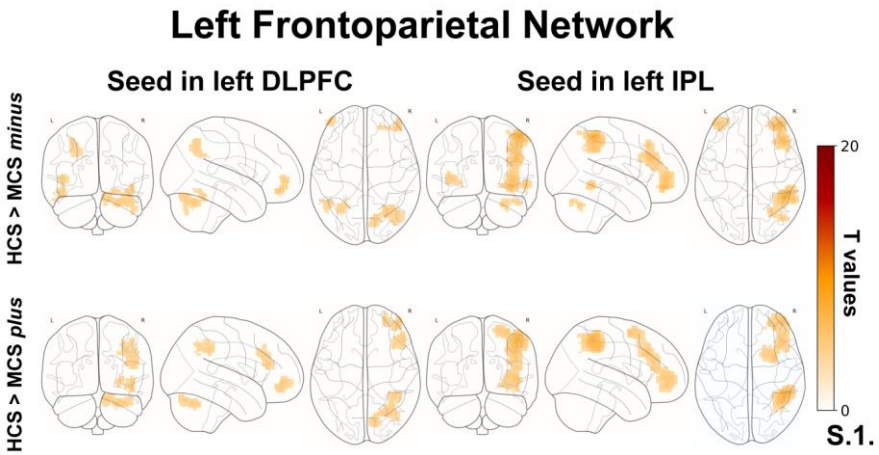


Figure S1. Comparison between HCS and patients of the correlation between the left DLPFC (left column) / IPL (right column) and the time series from all other brain voxels. Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. DLPFC: dorsolateral prefrontal cortex, IPL: inferior parietal lobule, MCS: minimally conscious state, HCS: healthy control subjects.

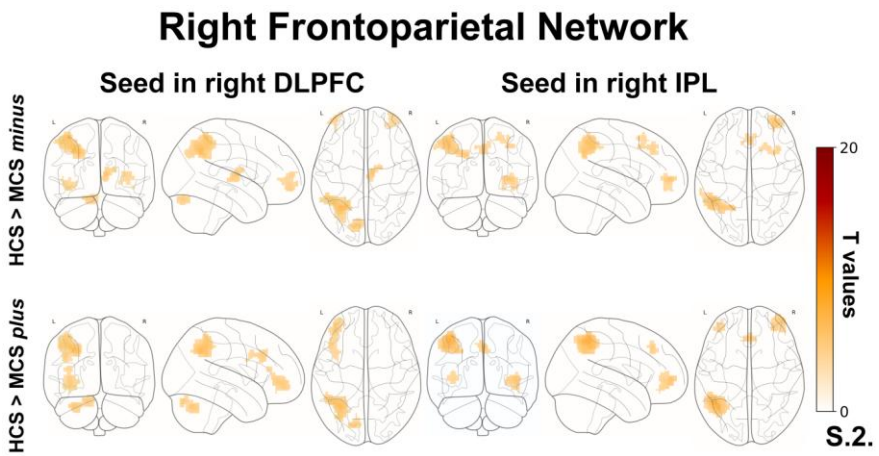


Figure S2. Comparison between HCS and patients of the correlation between the right DLPFC (left column) / IPL (right column) and the time series from all other brain voxels. Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. DLPFC: dorsolateral prefrontal cortex, IPL: inferior parietal lobule, MCS: minimally conscious state, HCS: healthy control subjects.

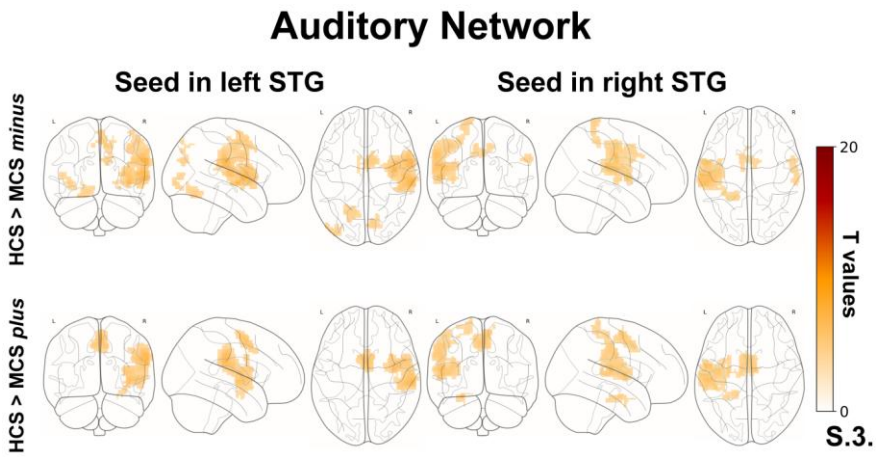


Figure S3. Comparison between HCS and patients of the correlation between the right (left column)/left STG (right column) and the time series from all other brain voxels. Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001(whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. STG: superior temporal gyrus, MCS: minimally conscious state, HCS: healthy control subjects.

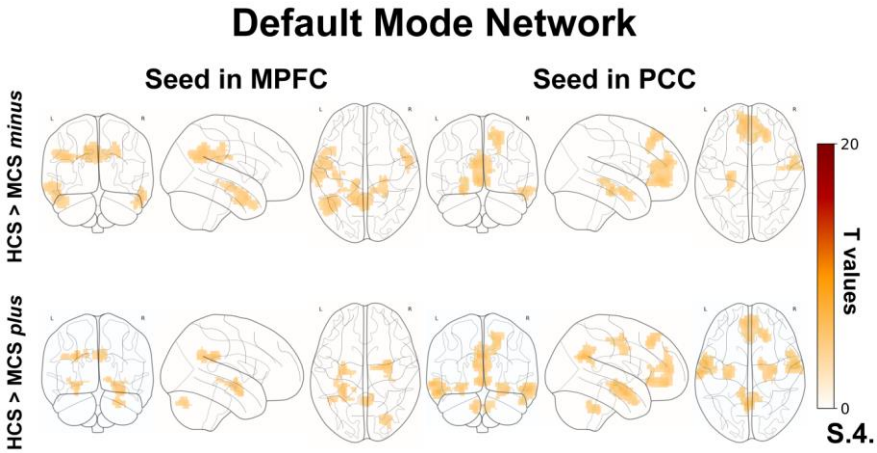


Figure S4. Comparison between HCS and patients of the correlation between the MPFC (left column)/PCC (right column) and the time series from all other brain voxels. Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. MPFC: anterior cingulate cortex, PCC: posterior cingulate cortex, MCS: minimally conscious state, HCS: healthy control subjects.

- Effect-sizes and confidence interval for all investigated seeds

Resting state fMRI analysis : Effect-sizes and confidence intervals (90%)

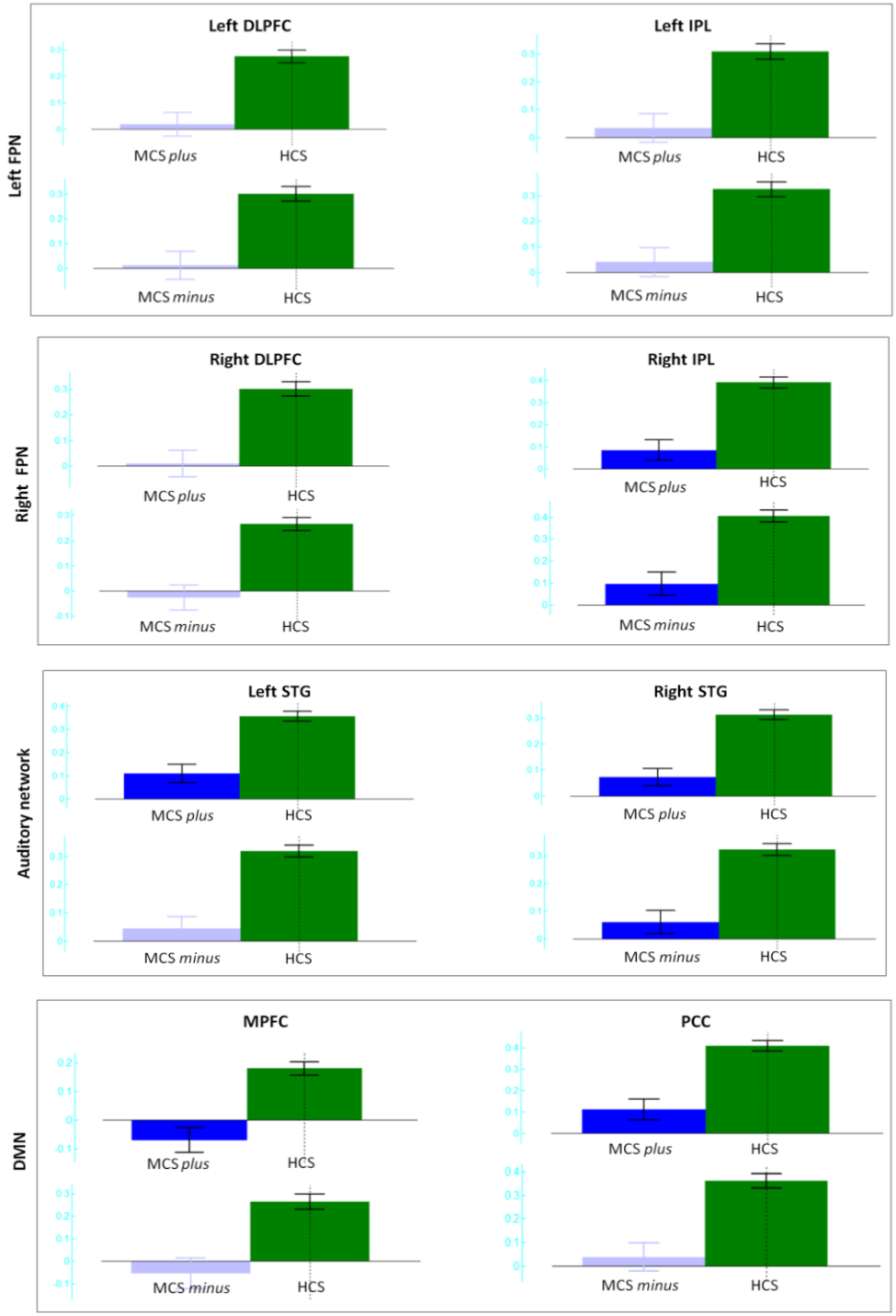


Figure S5. Summary of the differences of seed-based average correlations between MCS+ or MCS-

groups against the HCS group for multiple seeds (per row) and multiple target regions (per column). The first bar represents mean contrast estimates with 90% confidence interval in MCS- or MCS+ patients (blue); the second bar represents mean contrast estimates with 90% confidence interval in HCS (green). Statistical maps were thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level). MCS: minimally conscious state, HCS: healthy control subjects.

- Voxel-based morphometry analysis :

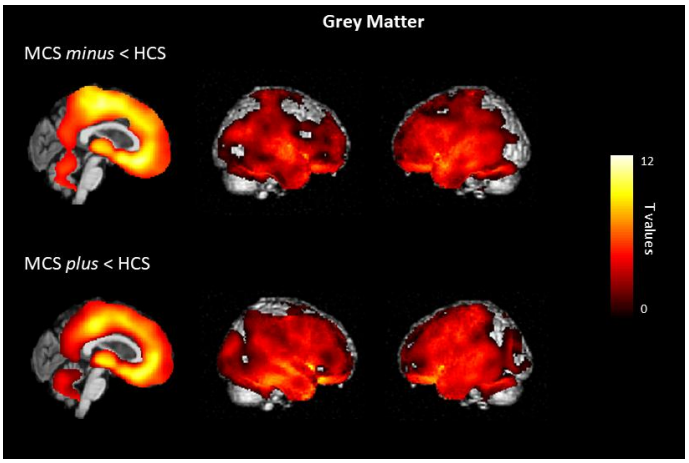


Figure S6. Grey matter volume decreases in MCS- (upper row) and MCS+ (bottom row) compared to HCS. Statistical maps are thresholded at p< 0.05 false discovery rate corrected and superimposed on an averaged rendered single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. MCS: minimally conscious state, HCS: healthy control subjects.

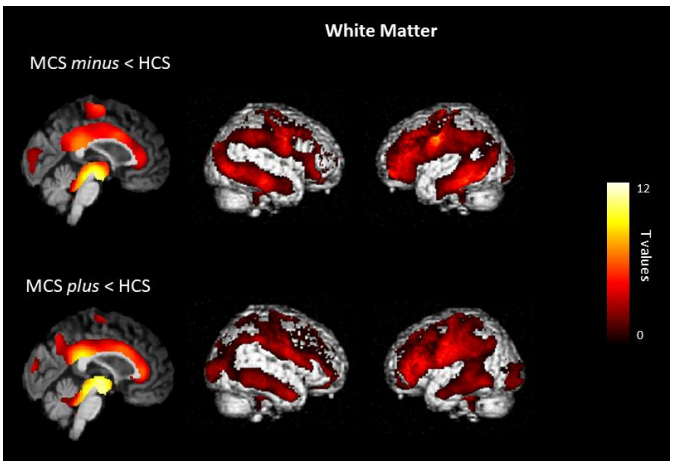


Figure S7. White matter volume decreases in MCS- (upper row) and MCS+ (bottom row) compared to HCS. Statistical maps are thresholded at p< 0.05 false discovery rate corrected and superimposed on an averaged rendered single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. MCS: minimally conscious state, HCS: healthy control subjects.

Appendix III

Supplementary Material 3

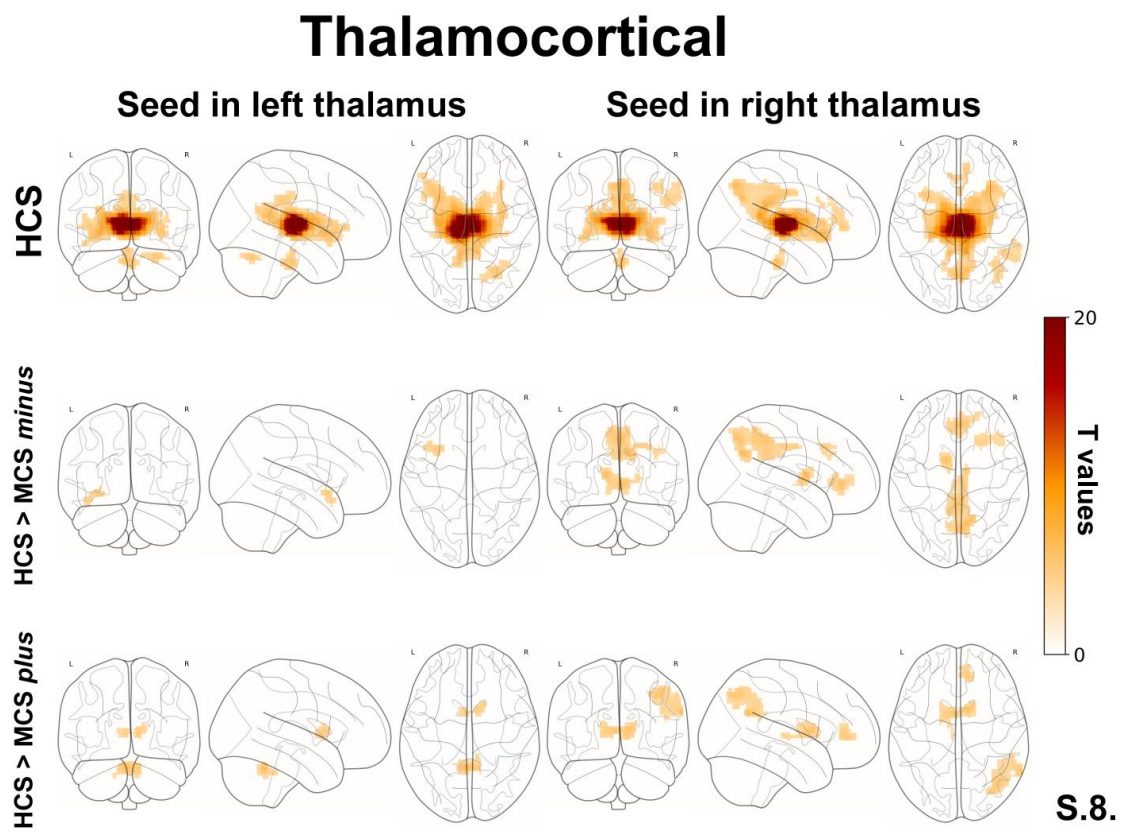


Figure S8. Correlation between the left (left column) and right (right column) thalami and the time series from all other brain voxels: not contrasted functional thalamocortical connectivity in HCS (healthy control subjects; upper row) and comparison between HCS and MCS (minimally conscious state) minus patients (middle row), as well as between HCS and MCS+ patients (bottom row). Statistical maps are thresholded at $p<0.05$ family wise error corrected at cluster level, with clusters made of voxels surviving a $p<0.001$ (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention.

Supplementary Material 4

Table S3. ROI to ROI interhemispheric connectivity analysis in patients as compared to healthy control subjects (HCS)

HCS > MCS-				HCS > MCS+			
Analysis unit	**Statistic**	**p-unc**	**p-FDR**	**Analysis unit**	**Statistic**	**p-unc**	**p-FDR**
Seed ACC	F(39) = 8.08 Intensity = 11.76 Size = 3	0.0000	0.0000	Seed ACC	F(40) = 7.32 Intensity = 9.90 Size = 3	0.0000	0.0001
ACC-PCC	T(45) = 4.72	0.0000	0.0002	ACC-PCC	T(46) = 3.95	0.0003	0.0019
ACC-DLPFC left	T(45) = -3.82	0.0004	0.0014	ACC-DLPFC left	T(46) = -3.18	0.0026	0.0092
ACC-DLPFC right	T(45) = -3.22	0.0024	0.0056	ACC-DLPFC right	T(46) = -2.77	0.0081	0.0189
Seed STG right	F(39) = 5.39 Intensity = 5.30 Size = 1	0.0002	0.0009	Seed STG left	F(40) = 6.30 Intensity = 5.53 Size = 1	0.0001	0.0002
STG right-STG left	T(45) = 5.30	0.0000	0.0000	STG left-STG right	T(46) = 5.53	0.0000	0.0000
Seed PCC	F(39) = 4.32 Intensity = 4.72 Size = 1	0.0013	0.0031	Seed IPL right	F(40) = 5.94	0.0001	0.0002
PCC-ACC	T(45) = 4.72	0.0000	0.0002	IPL right-IPL left	T(46) = 5.10	0.0000	0.0000
Seed STG left	F(39) = 4.21 Intensity = 5.30 Size = 1	0.0015	0.0031	Seed DLPFC right	F(40) = 5.38 Intensity = 7.21 Size = 2	0.0002	0.0004
STG left-STG right	T(45) = 5.30	0.0000	0.0000	DLPFC right-DLPFC left	T(46) = 4.45 T(46) = -2.77	0.0001 0.0081	0.0004 0.0284
Seed DLPFC right	F(39) = 3.69 Intensity = 3.22 Size = 1	0.0038	0.0060	DLPFC right-ACC			
DLPFC right-ACC	T(45) = -3.22	0.0024	0.0167	Seed IPL left	F(40) = 4.84 Intensity = 5.10 Size = 1	0.0005	0.0008
Seed IPL right	F(39) = 3.57 Intensity = 4.09 Size = 1	0.0046	0.0060	IPL left-IPL right	T(46) = 5.10	0.0000	0.0000
IPL right-IPL left	T(45) = -3.22	0.0002	0.0012	Seed PCC	F(40) = 4.55 Intensity = 3.95 Size = 1	0.0008	0.0010
Seed IPL left	F(39) = 3.50 Intensity = 4.09 Size = 1	0.0052	0.0060	PCC-ACC	T(46) = 3.95	0.0003	0.0019
				Seed DLPFC left	F(40) = 4.46 Intensity = 7.63	0.0010	0.0010

IPL left-IPL right	T(45) = 4.09	0.0002	0.0012
Seed DLPFC left	F(39) = 3.13 Intensity = 3.82 Size = 1	0.0102	0.0102
DLPFC left-ACC	T(45) = -3.82	0.0004	0.0028

	Size = 2		
DLPFC left-DLPFC right	T(46) = 4.45	0.0001	0.0004
DLPFC left-ACC	T(46) = -3.18	0.0026	0.0092
Seed STG right	F(40) = 4.46 Intensity = 5.53 Size = 1	0.0010	0.0010
STG right-STG left	T(46) = 5.33	0.0000	0.0000

Supplementary Material 5

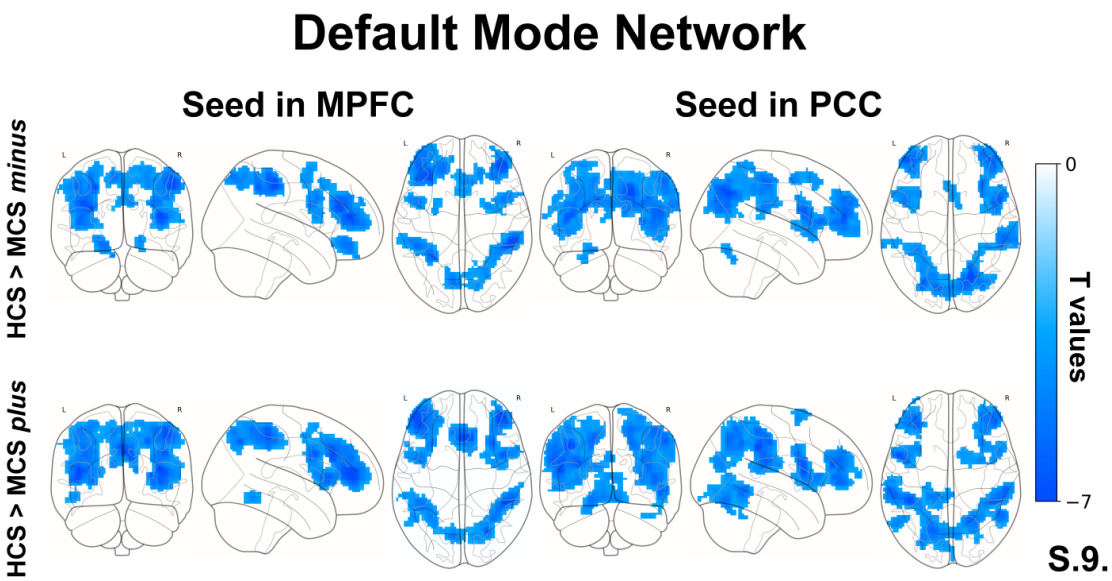


Figure S9. Comparison between HCS and patients of the anticorrelation between the mesioprefrontalcortex (MPFC), posterior cingulate cortex (PCC) and the time series from all other brain voxels. Statistical maps are thresholded at p<0.05 family wise error corrected at cluster level, with clusters made of voxels surviving a p<0.001 (whole-brain level) and are rendered on the midline and lateral surfaces of a single subject's MRI template. The colour bar indicates T values. This figure was displayed in neurological convention. MCS: minimally conscious state, HCS: healthy control subjects.

Reappearance of command-following is associated to recovery of language and consciousness networks: A longitudinal multiple-case report

Supplementary material

Supplementary material 1. Behavioral assessments based on repeated Coma Recovery Scale-Revised**.**

Supplementary material 2. Clusters emerging from the neuroimaging analyses**.**

Supplementary material 1. Behavioral assessments based on repeated CRS-R.

	Case 1		Case 2		Case 3	
	1st	2nd	1st	2nd	1st	2nd
AUDITORY FUNCTION						
4 – Consistent Movement to Command*						
3 – Reproducible Movement to Command*		X		X		X
2 – Localization to Sound	X					X
1 – Auditory Startle	X		X	X	X	X
0 – None						
VISUAL FUNCTION SCALE						
5 – Object Recognition*						
4 – Object Localization: Reaching*						
3 – Pursuit Eye Movements*		X	X	X	X	X
2 – Fixation*	X					
1 – Visual Startle			X	X	X	X
0 – None						
MOTOR FUNCTION SCALE						
6 – Functional Object Use †						
5 – Automatic Motor Response *						X
4 – Object Manipulation*						
3 – Localization to Noxious Stimulation*					X	
2 – Flexion Withdrawal	X	X	X	X	X	X
1 – Abnormal Posturing	X	X				X
0 – None/Flaccid						
OROMOTOR/ VERBAL FUNCTION SCALE						
3 – Intelligible Verbalization*						
2 – Vocalization/Oral Movement	X	X		X	X	X
1 – Oral Reflexive Movement	X	X	X	X		
0 – None						
COMMUNICATION SCALE						
2 – Functional: Accurate †						
1 – Non-Functional: intentional*						
0 – None	X	X	X	X	X	X
AROUSAL SCALE						
3 – Attention						
2 – Eye Opening w/o Stimulation		X	X	X	X	X
1 – Eye Opening with Stimulation	X	X	X	X	X	X
0 – Unarousable						
DIAGNOSIS	MCS-	MCS+	MCS-	MCS+	MCS-	MCS+

*MCS = minimally conscious state; * = behavioral sign of MCS; † = behavioral sign of emergence from the MCS.*

Supplementary material 2. Clusters emerging from the neuroimaging analyses.

	Cluster			Peak				Coordinates		
	p(FWE-corr)	equiv *k*	*p*(unc)	*p*(FWE-corr)	*p*(FDR-corr)	T	equiv *Z*	*x*	*y*	*z*
Case 1										
PET1	0.026	2666	0.008	0.000	0.000	7.349	5.762	4	-48	28
hypometabolism	0.092	1659	0.031	0.024	0.001	5.026	4.373	10	-72	-50
	0.651	291	0.336	0.090	0.004	4.510	4.011	-4	-104	0
	0.804	135	0.520	0.124	0.006	4.373	3.911	32	-98	-2
	0.218	1037	0.078	0.133	0.006	4.344	3.889	44	-66	48
	0.137	1367	0.047	0.140	0.006	4.320	3.872	-40	-72	44
	0.269	893	0.100	0.186	0.008	4.195	3.778	-28	-46	-8
	0.903	41	0.744	0.564	0.021	3.594	3.313	14	-24	10
	0.571	383	0.270	0.628	0.023	3.513	3.249	-32	10	54
	0.929	18	0.843	0.653	0.024	3.482	3.223	-10	16	30
	0.896	47	0.724	0.820	0.033	3.250	3.034	70	-26	0
	0.924	22	0.823	0.854	0.036	3.194	2.987	32	-44	-8
	0.905	39	0.751	0.898	0.041	3.106	2.913	66	-8	-12
	0.928	19	0.838	0.921	0.044	3.051	2.867	48	8	52
PET2	0.109	2022	0.028	0.000	0.000	7.176	5.670	4	-34	32
hypometabolism	0.196	1507	0.053	0.000	0.000	6.721	5.423	34	-42	-6
	0.001	7461	0.000	0.000	0.000	6.518	5.307	-28	-46	-6
	0.257	1276	0.073	0.031	0.001	4.933	4.309	66	-2	-4
	0.937	74	0.675	0.231	0.004	4.094	3.703	-4	-104	0
	0.942	65	0.698	0.324	0.005	3.925	3.573	32	-98	-2

	0.966	24	0.831	0.344	0.006	3.894	3.549	38	-14	-8
	0.935	76	0.670	0.498	0.009	3.678	3.380	-14	-18	20
	0.958	39	0.774	0.643	0.013	3.495	3.234	34	62	-12
	0.939	70	0.685	0.697	0.014	3.425	3.177	-54	18	0
	0.960	35	0.788	0.842	0.022	3.213	3.003	64	-58	2
	0.974	11	0.896	0.925	0.031	3.040	2.858	30	28	-24
	0.978	6	0.929	0.933	0.032	3.018	2.839	-28	-100	-4
	0.975	9	0.908	0.944	0.035	2.983	2.810	-30	22	-34
	0.980	3	0.955	0.967	0.041	2.891	2.731	0	-18	20
	0.982	1	0.978	0.980	0.048	2.811	2.663	-32	62	-8
	0.982	1	0.978	0.981	0.048	2.809	2.661	58	-8	-38
	0.982	1	0.978	0.983	0.050	2.792	2.646	60	-4	-34
PET1 < PET2	0.183	1160	0.064	0.018	0.001	5.135	4.447	-4	-56	24
	0.225	1015	0.081	0.133	0.006	4.344	3.889	44	-66	48
	0.137	1367	0.047	0.140	0.006	4.320	3.872	-40	-72	44
	0.751	187	0.444	0.204	0.009	4.152	3.747	-34	-92	18
	0.766	172	0.464	0.421	0.016	3.780	3.461	-34	-56	-22
	0.872	70	0.656	0.548	0.020	3.614	3.329	34	-94	-2
	0.772	166	0.472	0.617	0.023	3.528	3.260	38	-72	-26
	0.571	383	0.270	0.628	0.023	3.513	3.249	-32	10	54
	0.936	12	0.878	0.733	0.028	3.378	3.138	-6	-102	-2
	0.947	4	0.939	0.879	0.039	3.146	2.947	70	-28	2
	0.949	3	0.950	0.890	0.040	3.123	2.927	-10	-104	-6
	0.944	6	0.921	0.902	0.041	3.097	2.906	-2	-100	-2

	0.951	2	0.961	0.905	0.041	3.091	2.901	-6	-104	10
	0.949	3	0.950	0.909	0.042	3.081	2.893	-22	-58	-12
	0.928	19	0.838	0.921	0.044	3.051	2.867	48	8	52
	0.951	2	0.961	0.926	0.044	3.038	2.856	16	-84	-32
	0.953	1	0.975	0.940	0.047	2.996	2.821	-10	-104	4
	0.953	1	0.975	0.953	0.049	2.951	2.783	12	-82	-32
Case 2										
PET1	0.000	43552	0.000	0.000	0.000	17.596	65535	-10	50	6
hypometabolism	1.000	10	0.943	0.000	0.000	7.687	5.934	-24	18	-36
	0.997	177	0.673	0.019	0.000	5.035	4.380	-8	-28	-46
	0.998	138	0.715	0.765	0.004	3.234	3.020	10	-76	-50
	1.000	7	0.955	0.921	0.008	2.949	2.781	36	62	-10
	1.000	16	0.923	0.986	0.017	2.654	2.527	44	-44	-50
	1.000	3	0.974	0.992	0.020	2.588	2.469	18	-102	-12
	1.000	2	0.980	0.998	0.028	2.431	2.330	34	64	-4
	1.000	1	0.988	1.000	0.045	2.229	2.150	-2	-34	4
	1.000	1	0.988	1.000	0.046	2.212	2.135	20	-100	-14
	1.000	1	0.988	1.000	0.049	2.187	2.112	32	64	-8
	1.000	1	0.988	1.000	0.049	2.185	2.111	42	54	-14
PET2	0.000	36836	0.000	0.000	0.000	17.321	65535	-10	50	4
hypometabolism	0.999	10	0.939	0.000	0.000	7.723	5.952	-24	18	-36
	0.994	172	0.658	0.000	0.000	6.461	5.274	46	-44	-46
	1.000	4	0.966	0.969	0.015	2.777	2.633	18	-102	-12
	0.999	8	0.947	0.996	0.029	2.500	2.391	16	-40	78

	1.000	1	0.987	1.000	0.049	2.266	2.183	18	-14	28
PET1 < PET2	0.040	8825	0.005	0.000	0.000	10.695	7.222	-32	2	-18
	0.999	45	0.853	0.000	0.000	9.206	6.636	-46	-18	-38
	0.997	193	0.657	0.003	0.000	5.751	4.847	-46	-42	-36
	0.997	177	0.673	0.019	0.000	5.035	4.380	-8	-28	-46
	0.997	182	0.668	0.021	0.000	4.991	4.349	6	50	-26
	0.998	117	0.740	0.130	0.000	4.259	3.826	16	12	-22
	1.000	1	0.988	0.280	0.001	3.906	3.559	-6	2	-20
	0.999	85	0.784	0.291	0.001	3.885	3.542	0	-28	0
	1.000	33	0.879	0.705	0.003	3.317	3.089	0	52	20
	0.998	138	0.715	0.765	0.004	3.234	3.020	10	-76	-50
	1.000	25	0.898	0.783	0.004	3.208	2.999	-4	0	-18
	1.000	19	0.914	0.855	0.006	3.090	2.900	16	-14	22
	1.000	7	0.955	0.921	0.008	2.949	2.781	36	62	-10
	1.000	5	0.964	0.953	0.011	2.847	2.694	18	66	-6
	1.000	1	0.988	0.996	0.025	2.491	2.383	4	60	16
	1.000	1	0.988	0.996	0.025	2.486	2.379	14	-2	-10
	1.000	1	0.988	0.997	0.026	2.473	2.367	8	-6	52
	1.000	1	0.988	0.997	0.028	2.445	2.343	-4	-12	-14
	1.000	2	0.980	0.998	0.028	2.431	2.330	34	64	-4
	1.000	1	0.988	0.998	0.029	2.430	2.330	-16	-14	-30
	1.000	1	0.988	0.998	0.029	2.416	2.317	-24	-60	-22
	1.000	1	0.988	0.998	0.031	2.394	2.298	-18	-38	-20
	1.000	1	0.988	0.999	0.032	2.385	2.290	12	-6	-12

	1.000	1	0.988	0.999	0.039	2.295	2.210	28	66	-4
	1.000	1	0.988	1.000	0.045	2.230	2.151	2	54	28
	1.000	1	0.988	1.000	0.045	2.230	2.151	-2	-60	40
	1.000	1	0.988	1.000	0.045	2.229	2.150	-2	-34	4
	1.000	1	0.988	1.000	0.046	2.212	2.135	20	-100	-14
	1.000	1	0.988	1.000	0.048	2.196	2.120	22	28	-24
	1.000	1	0.988	1.000	0.049	2.187	2.112	32	64	-8
	1.000	1	0.988	1.000	0.049	2.185	2.111	42	54	-14
VBM1< VBM2	0.000	44386	0.000	0.001	0.000	15.207	5.733	-8	10	-12
	1.000	103	0.646	0.050	0.001	8.669	4.669	23	9	18
	0.960	696	0.210	0.273	0.001	6.597	4.115	-41	-65	-12
	0.999	277	0.430	0.775	0.004	5.066	3.566	-63	-53	-12
	0.999	236	0.468	0.878	0.006	4.745	3.430	-68	-27	-20
	1.000	173	0.540	1.000	0.029	3.263	2.672	-50	-65	39
Case 3										
PET1	0.000	71242	0.000	0.000	0.000	8.122	6.147	-40	4	56
hypometabolism	1.000	4	0.971	1.000	0.039	2.197	2.121	14	-24	18
	1.000	2	0.982	1.000	0.042	2.154	2.082	10	-18	20
	1.000	1	0.989	1.000	0.049	2.068	2.004	-58	-8	18
PET2	0.000	18568	0.000	0.000	0.000	10.561	7.173	-12	-22	8
hypometabolism	0.985	38	0.800	0.001	0.000	6.144	5.088	-18	-26	18
	0.993	5	0.944	0.103	0.001	4.450	3.967	-12	-20	-12
	0.994	1	0.980	0.540	0.006	3.622	3.335	-8	-20	20
	0.974	80	0.693	0.728	0.010	3.382	3.142	-62	6	12

	0.981	53	0.757	0.867	0.017	3.167	2.965	-56	-6	48
PET1 < PET2	0.000	59167	0.000	0.000	0.000	8.122	6.147	-40	4	56
	1.000	48	0.858	0.380	0.001	3.837	3.505	18	-8	24
	1.000	105	0.773	0.530	0.002	3.635	3.346	-14	8	14
	1.000	3	0.976	0.999	0.023	2.450	2.347	-20	12	2
	1.000	4	0.971	1.000	0.039	2.197	2.121	14	-24	18
	1.000	1	0.989	1.000	0.042	2.157	2.085	-12	-36	46
	1.000	2	0.982	1.000	0.042	2.154	2.082	10	-18	20
	1.000	1	0.989	1.000	0.047	2.090	2.025	-26	-64	-16
	1.000	1	0.989	1.000	0.049	2.068	2.004	-58	-8	18
VBM1 < VBM2	0.998	216	0.418	0.431	0.019	6.126	3.961	17	-7	14
	0.082	3092	0.006	0.463	0.019	6.030	3.928	-66	-56	-9
	0.049	3580	0.003	0.490	0.019	5.952	3.901	2	-42	59
	0.980	402	0.267	0.602	0.019	5.647	3.792	-11	17	63
	0.963	480	0.226	0.636	0.020	5.558	3.759	66	-51	-2
	0.436	1546	0.039	0.650	0.020	5.522	3.745	21	-4	-18
	0.608	1207	0.064	0.677	0.020	5.451	3.718	-51	18	-30
	0.992	304	0.334	0.755	0.020	5.246	3.638	-23	-24	-35
	0.276	1974	0.022	0.862	0.021	4.931	3.509	-38	-4	62
	0.588	1243	0.061	0.872	0.021	4.896	3.495	-44	-68	51
	1.000	128	0.540	0.954	0.023	4.533	3.335	-24	-24	-12
	1.000	129	0.539	0.979	0.024	4.329	3.240	-17	9	15
	0.998	223	0.410	0.994	0.027	4.090	3.123	32	48	3

Brain, behavior and cognitive interplay in disorders of consciousness: A multiple case study

Supplementary material

Supplementary material 1. CAVE scoring form**.**

Supplementary material 2. Significant clusters emerging from the analyses**.**

COGNITIVE ASSESSMENT BY VISUAL ELECTION

NAME: ..... DATE .....

A. REAL OBJECTS			
1. Ball		BUS	
2. CUP		Comb	
3. Cow		PIG	
4. Bus		CAR	
5. PEN		Fork	
6. Car		COW	
7. SPOON		Cup	
8. COMB		Pen	
9. FORK		Spoon	
10. Pig		BALL	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

B. NUMBERS			
1. 5		8	
2. 3		9	
3. 1		7	
4. 4		2	
5. 6		3	
6. 8		4	
7. 0		5	
8. 7		2	
9. 6		0	
10. 9		1	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

C. WORDS			
1. COMB		Pen	
2. Bus		CAR	
3. SPOON		Cup	
4. PEN		Fork	
5. Car		COW	
6. Ball		BUS	
7. CUP		Comb	
8. Pig		BALL	
9. FORK		Spoon	
10. Cow		PIG	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

D. LETTERS			
1. H		R	
2. A		L	
3. B		F	
4. G		B	
5. C		W	
6. L		Z	
7. F		H	
8. R		G	
9. W		A	
10. Z		C	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

E. PICTURES			
1. Car		COW	
2. Pig		BALL	
3. CUP		Comb	
4. Ball		BUS	
5. FORK		Spoon	
6. COMB		Pen	
7. Cow		PIG	
8. Bus		CAR	
9. PEN		Fork	
10. SPOON		Cup	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

F. COLOURS			
1. BLUE		White	
2. Orange		BLACK	
3. Pink		GREEN	
4. GREY		Red	
5. Green		ORANGE	
6. Yellow		PINK	
7. PURPLE		Grey	
8. Black		YELLOW	
9. RED		Blue	
10. WHITE		Purple	
Total Left:		Right:	
Grand total:			
Pass/Fail:			

Supplementary material 2 – Significant clusters

Table S1: Significant clusters emerging after the VBM (grey matter) and PET analyses.

		Set		Cluster				Peak				Coordinates		
Case	Analysis	*p*	*c*	*p*(FWE-corr)	*p*(FDR-corr)	equiv *k*	*p*(unc)	*p*(FWE-corr)	*p*(FDR-corr)	*T*	equiv *Z*	*x*	*y*	*z*
Case 1	Grey matter reduction	0,001	9	0,000	0,000	18041	0,000	0,002	0,034	6,393	5,120	-30	-15	-17
	Hypometabolism	0,000	9	0,016	0,033	1115	0,007	0,030	0,125	5,300	4,462	-46	-70	38
				0,015	0,033	1137	0,007	0,038	0,125	5,200	4,395	-8	-18	6
				0,606	0,550	80	0,428	0,164	0,336	4,500	3,965	26	18	50
				0,247	0,390	298	0,130	0,294	0,336	4,200	3,757	-62	-24	-6
				0,559	0,550	99	0,376	0,300	0,336	4,200	3,750	-48	-6	-34
				0,550	0,550	103	0,366	0,369	0,370	4,100	3,666	-30	-12	0
				0,540	0,550	107	0,357	0,441	0,416	4,000	3,588	-48	0	52
				0,800	0,832	17	0,739	0,752	0,689	3,600	3,270	-32	-88	28
				0,851	0,875	5	0,875	0,879	0,971	3,400	3,103	12	-90	8
				0,801	0,850	14	0,773	0,771	0,790	3,400	3,229	34	-18	-20
				0,857	0,932	2	0,932	0,866	0,962	3,300	3,106	-6	-54	22
	Preserved metabolism	0,024	6	0,000	0,000	3392	0,000	0,000	0,002	7,200	5,534	26	24	24
				0,233	0,243	313	0,122	0,141	0,219	4,600	4,013	-22	46	-4
				0,041	0,058	803	0,019	0,172	0,219	4,500	3,948	48	-48	32
				0,336	0,282	221	0,188	0,247	0,219	4,300	3,823	36	2	-42
				0,488	0,369	131	0,308	0,304	0,222	4,200	3,745	-34	32	20
				0,554	0,371	101	0,371	0,583	0,428	3,800	3,445	20	-54	54
Case 2	Grey matter	0,000	18	0,000	0,000	27549	0,000	0,000	0,000	11,546	7,258	-29	-15	-24

	reduction													
				0,000	0,000	11630	0,000	0,000	0,000	8,075	5,958	-8	27	-12
				0,002	0,004	3881	0,001	0,005	0,006	6,073	4,941	68	-9	-9
				0,039	0,046	1634	0,015	0,027	0,022	5,369	4,519	-11	-26	36
				0,035	0,046	1701	0,014	0,090	0,058	4,857	4,188	-11	-60	11
				0,038	0,046	1657	0,015	0,280	0,161	4,326	3,822	23	-77	-30
	Hypometabolism	0,082	4	0,000	0,000	23919	0,000	0,000	0,000	15,600	65535,000	-54	-26	36
				0,671	0,958	26	0,684	0,455	0,382	3,800	3,466	32	6	-46
				0,709	0,958	16	0,760	0,658	0,665	3,600	3,256	-2	-36	-50
				0,789	0,958	1	0,958	0,801	0,995	3,400	3,093	4	24	18
	Preserved metabolism	0,803	1	0,000	0,000	62424	0,000	0,000	0,000	13,100	7,703	34	2	-24
Case 3	Grey matter reduction	0,000	18	0,004	0,030	3129	0,002	0,007	0,118	5,919	4,852	20	-6	-20
				0,025	0,086	1916	0,010	0,120	0,481	4,737	4,107	-27	-4	53
				0,036	0,086	1687	0,014	0,124	0,481	4,722	4,098	-15	-6	-12
	Hypometabolism	0,000	10	0,000	0,000	7400	0,000	0,000	0,000	12,200	7,465	-28	-18	68
				0,003	0,004	1772	0,001	0,000	0,000	9,200	6,429	34	34	38
				0,109	0,088	515	0,053	0,002	0,004	6,400	5,117	26	-8	-28
				0,012	0,011	1208	0,006	0,005	0,009	6,000	4,886	26	-28	70
				0,006	0,007	1484	0,003	0,012	0,018	5,600	4,691	-32	-90	8
				0,002	0,004	1822	0,001	0,015	0,021	5,500	4,631	2	-24	-4
				0,543	0,452	105	0,362	0,207	0,147	4,400	3,884	-14	14	12
				0,163	0,117	405	0,082	0,384	0,274	4,100	3,647	36	-70	-34
				0,791	0,757	19	0,722	0,653	0,538	3,700	3,372	-66	-34	34
				0,806	0,757	15	0,757	0,798	0,763	3,500	3,214	36	-88	8

Appendix V

	Preserved metabolism	0,023	6	0,000	0,000	7051	0,000	0,000	0,000	9,100	6,399	46	-2	18
				0,000	0,000	5503	0,000	0,000	0,000	9,100	6,379	-50	-28	30
				0,199	0,205	352	0,102	0,244	0,199	4,300	3,825	-38	2	-32
				0,410	0,365	172	0,243	0,358	0,222	4,100	3,676	12	36	36
				0,628	0,548	71	0,457	0,360	0,222	4,100	3,674	-14	36	2
				0,794	0,731	18	0,731	0,754	0,648	3,600	3,265	16	48	-12
Case 4	Grey matter reduction	0,000	18	0,000	0,003	4948	0,000	0,001	0,017	6,543	5,202	30	-4	-20
	Hypometabolism	0,023	6	0,000	0,000	31770	0,000	0,000	0,000	8,500	6,138	44	10	50
				0,013	0,012	1182	0,006	0,000	0,002	7,100	5,475	-16	12	8
				0,000	0,000	2838	0,000	0,001	0,003	6,500	5,195	-50	-68	18
				0,126	0,075	472	0,062	0,011	0,009	5,700	4,713	36	-20	-20
				0,020	0,014	1024	0,010	0,104	0,065	4,700	4,107	4	-50	34
				0,443	0,271	152	0,271	0,234	0,139	4,400	3,840	-34	-20	-18
	Preserved metabolism	0,000	13	0,000	0,000	3637	0,000	0,000	0,000	10,000	6,751	-30	-8	18
				0,006	0,011	1486	0,003	0,000	0,000	9,800	6,680	32	-4	18
				0,000	0,000	10537	0,000	0,000	0,002	7,000	5,454	20	-56	-20
				0,198	0,265	352	0,102	0,065	0,074	4,900	4,244	32	2	-28
				0,124	0,200	475	0,062	0,097	0,102	4,800	4,125	12	-28	58
				0,680	0,930	52	0,528	0,377	0,393	4,100	3,654	22	36	8
				0,528	0,752	111	0,347	0,426	0,406	4,000	3,601	-12	-88	10
				0,834	0,930	8	0,833	0,678	0,663	3,700	3,346	-68	-18	6
				0,809	0,930	14	0,766	0,682	0,663	3,700	3,342	-52	-62	-30
				0,860	0,930	3	0,909	0,702	0,673	3,600	3,321	-18	-6	-34
				0,805	0,930	15	0,757	0,763	0,741	3,600	3,254	-36	-2	-24

				0,854	0,930	4	0,891	0,825	0,865	3,500	3,178	-20	38	4
				0,866	0,930	2	0,930	0,857	0,919	3,400	3,134	-20	-4	-36
Case 5	Grey matter reduction	0,000	14	0,000	0,000	19894	0,000	0,000	0,001	8,041	5,943	-53	-69	-9
				0,001	0,003	4300	0,000	0,040	0,078	5,202	4,413	11	-1	65
	Hypometabolism	0,475	2	0,000	0,000	37018	0,000	0,000	0,000	15,400	65535,000	-54	-58	20
				0,555	0,507	65	0,507	0,109	0,072	4,600	3,993	52	-70	14
	Preserved metabolism	0,798	1	0,000	0,000	68590	0,000	0,000	0,000	17,300	65535,000	34	0	-28

Appendix V

[redacted]

Validation of the Brief Evaluation of Receptive Aphasia for detection of specific language impairment in severely brain-injured patients

Supplementary material

Supplementary material 1. BERA scoring forms**.**

Supplementary material 2. Examples of BERA images.

BRIEF EVALUATION OF RECEPTIVE APHASIA (BERA)

Version 1

P1	**Mont**	Gant	
S6	Ours	**Renne**	
M1	Elle marche.	**Elle chante.**	
P6	Cou	**Roux**	
S1	**Trompette**	Botte	
M6	**Le garçon est suivi par le chien.**	Le garçon suit le chien.	
P2	Banc	**Veau**	
S7	**Ananas**	Cerises	
M2	Nicolas est triste.	**Nicolas est joyeux.**	
P7	Main	**Nain**	
S2	Chausson	**Cabane**	
M7	Le chien tire l'enfant.	**L'enfant tire le chien.**	
P3	**Vent**	Seau	
S8	Œil	**Oreille**	
M3	**La fille mange une pomme**	La fille pèle une poire.	
P8	**Chou**	Sous	
S3	**Igloo**	Biche	
M8	Elle dort.	**Elles dorment.**	
P4	**Peau**	Mie	
S9	Cactus	**Tulipe**	
M4	Il apporte sa valise.	**Il nourrit son chat.**	
P9	**Riz**	Rat	
S4	**Chèvre**	Echarpe	
M9	**Le chien est derrière la maison**	Le chien est devant la maison.	
P5	Quille	**Mue**	
S10	Scie	**Ciseaux**	
M5	**Ils promènent leur enfant.**	Ils promènent leur chien.	
P10	Pont	**Pas**	
S5	**Ceinture**	Guitare	
M10	**Tous les chats sont gris.**	Certains chats sont gris.	

Total gauche	/15	Total droite :	/15
Total phonologie simple:	/5	Total phonologie complexe :	/5
Total sémantique simple	/5	Total sémantique complexe :	/5
Total morphosyntaxe simple	/5	Total morphosyntaxe complexe :	/5
Total			**/30**

BRIEF EVALUATION OF RECEPTIVE APHASIA (BERA)

Version 2

P1	**Rue**	Nœud	
S6	Pantalon	**Gilet**	
M1	Emilie pleure.	**Emilie court.**	
P6	Paon	**Champ**	
S1	**Chaise**	Brouette	
M6	**L'homme est soigné par la femme.**	L'homme soigne la femme.	
P2	**Queue**	Dé	
S7	**Marron**	Noisettes	
M2	Il est fâché.	**Il est content.**	
P7	**Bond**	Rond	
S2	Râteau	**Pieuvre**	
M7	Le camion écrase la voiture.	**La voiture écrase le camion.**	
P3	Thé	**Long**	
S8	Assiette	**Fourchette**	
M3	**Le garçon porte un manteau.**	Le garçon met ses chaussures.	
P8	Chat	**Mat**	
S3	**Crabe**	Gâteau	
M8	**Elle lit.**	Elles lisent.	
P4	Lit	**Daim**	
S9	Voiture	**Vélo**	
M4	Elle attend le bus.	**Elle nourrit son chat.**	
P9	Fée	**Fût**	
S4	**Gaufre**	Lunettes	
M9	**Le chat est sur la chaise.**	Le chat est sous la chaise.	
P5	**Rein**	Vue	
S10	Talon	**Poignet**	
M5	**Elles écrivent une lettre.**	Elles écrivent au tableau.	
P10	**Lent**	Loup	
S5	**Loupe**	Table	
M10	Le bébé a reçu peu de peluches.	**Le bébé a reçu beaucoup de peluches.**	

Total gauche	/15	Total droite :	/15
Total phonologie simple:	/5	Total phonologie complexe :	/5
Total sémantique simple	/5	Total sémantique complexe :	/5
Total morphosyntaxe simple	/5	Total morphosyntaxe complexe :	/5
Total			**/30**

BRIEF EVALUATION OF RECEPTIVE APHASIA (BERA)

Version 3

P1	Cou	**Nain**	
S6	**Trompette**	Guitare	
M1	Elle rit.	**Elle pense.**	
P6	Mont	**Mue**	
S1	**Ours**	Cerises	
M6	Claire est soulevée par Adrien.	**Claire soulève Adrien.**	
P2	**Main**	Sous	
S7	**Chausson**	Botte	
M2	**Nicolas est à l'heure.**	Nicolas est en retard.	
P7	Banc	**Gant**	
S2	Ananas	**Oreille**	
M7	**Le chat mord le chien.**	Le chien mord le chat.	
P3	**Chou**	Rat	
S8	**Igloo**	Cabane	
M3	**La fille prend le bus.**	La fille met une veste.	
P8	**Vent**	Veau	
S3	Œil	**Tulipe**	
M8	Il conduit.	**Ils conduisent.**	
P4	Riz	**Pas**	
S9	Chèvre	**Biche**	
M4	Il remplit sa valise	**Il caresse son chat.**	
P9	**Mie**	Quille	
S4	Cactus	**Ciseaux**	
M9	**L'oiseau est près de la fille.**	L'oiseau est loin de la fille.	
P5	**Pont**	Roux	
S10	Ceinture	**Echarpe**	
M5	**Ils emballent le coffret.**	Ils emballent les fleurs.	
P10	Peau	**Seau**	
S5	**Scie**	Renne	
M10	Pas un homme ne circule dans la rue.	**Plus d'un homme circule dans la rue.**	

Total gauche	/15	Total droite :	/15
Total phonologie simple:	/5	Total phonologie complexe :	/5
Total sémantique simple	/5	Total sémantique complexe :	/5
Total morphosyntaxe simple	/5	Total morphosyntaxe complexe :	/5
Total			**/30**

Appendix VI

BRIEF EVALUATION OF RECEPTIVE APHASIA (BERA)

Version 4

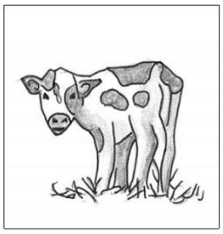
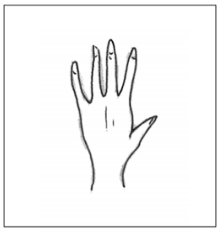
P1	**Paon**	Rond	
S6	**Chaise**	Table	
M1	Emilie rêve.	**Emilie nage.**	
P6	Rue	**Vue**	
S1	**Pantalon**	Noisettes	
M6	**Le garçon est appelé par la fille.**	Le garçon appelle la fille.	
P2	**Bond**	Mat	
S7	Râteau	**Brouette**	
M2	Elle est grande.	**Elle est petite.**	
P7	**Queue**	Nœud	
S2	Marron	**Fourchette**	
M7	Le voleur blesse le policier.	**Le policier blesse le voleur.**	
P3	Chat	**Fût**	
S8	**Crabe**	Pieuvre	
M3	**Le garçon fait la lessive.**	Le garçon prépare le repas.	
P8	**Thé**	Dé	
S3	Assiette	**Vélo**	
M8	**Elle boit.**	Elles boivent.	
P4	Fée	**Lent**	
S9	**Gaufre**	Gâteau	
M4	Il perd ses clés.	**Il trouve un trésor.**	
P9	**Lit**	Long	
S4	Voiture	**Poignet**	
M9	**La table est dans la salle.**	La table est hors de la salle.	
P5	Loup	**Champ**	
S10	**Loupe**	Lunettes	
M5	**Elles regardent la télévision.**	Elles regardent des photos.	
P10	Rein	**Daim**	
S5	Talon	**Gilet**	
M10	Justine enfile tous les colliers.	**Justine enfile certains colliers.**	

Total gauche	/15	Total droite :	/15
Total phonologie simple:	/5	Total phonologie complexe :	/5
Total sémantique simple	/5	Total sémantique complexe :	/5
Total morphosyntaxe simple	/5	Total morphosyntaxe complexe :	/5
Total			**/30**

Examples of BERA images:

- Phonology:

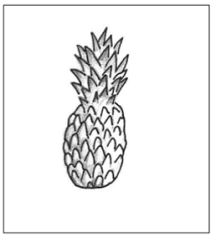
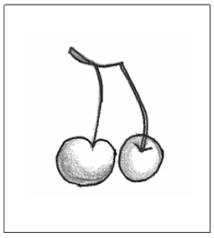
Simple Complex


- Semantics:

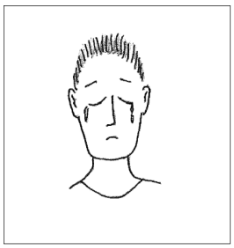
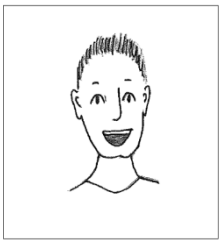
Simple Complex

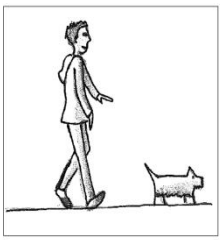


- Morphosyntax

Simple Complex



Language impairment such as receptive aphasia might lead to an underestimation of the level of consciousness in post-comatose patients (Schnakers et al., 2014). Yet, only a few studies focused on the behavioral assessment of residual language function, as based on the Coma Recovery Scale-Revised (CRS-R) and other tools, in line with their neural correlates. As previously recommended by Majerus et al. (2009), we here combined such behavioral and neuroimaging assessments to better explore language functions in patients with disorders of consciousness.

In the **Experimental part I**, we investigated the neural correlates of the clinical sub-categorization of minimally conscious state (MCS), based on the presence (i.e., MCS+) or absence (i.e., MCS-) of language-related signs of consciousness. As expected, language areas were shown to be more activated in MCS+ compared to MCS-, either using resting state FDG-PET or fMRI. These areas mainly encompassed the left-sided temporal lobule, angular gyrus, inferior/middle frontal cortex, caudate and temporo-occipital fusiform cortex. We also observed increased connectivity in the left frontoparietal network in MCS+ compared to MCS- patients, which was previously associated to language function. This result was particularly consistent across studies, either according to FDG-PET or fMRI measurements. Hence, MCS patients and healthy subjects could be placed along a continuum, from severe left frontoparietal network dysfunction, possibly associated to severely impaired language processing in MCS- patients, to preserved network connectivity in healthy subjects, with MCS+ patients being situated between these two groups. By contrast, increase of grey matter volume as assessed by voxel-based morphometry analyses was not significantly associated to the recovery of command-following, intelligible verbalization and/or intentional communication, unless at the individual-level. Finally, with regard to consciousness areas, a lower impairment of default mode network areas in MCS+ compared to MCS- was only revealed at the single subject-level. The MCS sub-categorization would thus reflect distinct levels of language impairments more than different levels of consciousness

The **Experimental part II** presents new bedside language assessments to complement the CRS-R and neuroimaging examinations. The Cognitive Assessment by Visual Election (CAVE) comprises tasks involving semantic and reading abilities (i.e., recognition of objects, pictures, letters, numbers, written words and colors), whereas the Brief Evaluation of Receptive Aphasia (BERA) is composed of three subscales examining different domains of language: phonology, semantics and morphosyntax. Good psychometric properties (reliability, validity and sensitivity) were shown using the BERA in aphasic conscious patients.The use of both tools in addition to the CRS-R in patients with disorders of consciousness allowed refining their behavioral language profiles, which were in line with FDG-PET and structural MRI results.