Relationship between etiology and covert cognition in the minimally conscious state

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ABSTRACT

Objectives: Functional neuroimaging has shown that the absence of externally observable signs of consciousness and cognition in severely brain-injured patients does not necessarily indicate the true absence of such abilities. However, relative to traumatic brain injury, nontraumatic injury is known to be associated with a reduced likelihood of regaining overtly measurable levels of consciousness. We investigated the relationships between etiology and both overt and covert cognitive abilities in a group of patients in the minimally conscious state (MCS).

Methods: Twenty-three MCS patients (15 traumatic and 8 nontraumatic) completed a motor imagery EEG task in which they were required to imagine movements of their right-hand and toes to command. When successfully performed, these imagined movements appear as distinct sensorimotor modulations, which can be used to determine the presence of reliable command-following. The utility of this task has been demonstrated previously in a group of vegetative state patients.

Results: Consistent and robust responses to command were observed in the EEG of 22% of the MCS patients (5 of 23). Etiology had a significant impact on the ability to successfully complete this task, with 33% of traumatic patients (5 of 15) returning positive EEG outcomes compared with none of the nontraumatic patients (0 of 8).

Conclusions: The overt behavioral signs of awareness (measured with the Coma Recovery Scale–Revised) exhibited by nontraumatic MCS patients appear to be an accurate reflection of their covert cognitive abilities. In contrast, one-third of a group of traumatically injured patients in the MCS possess a range of high-level cognitive faculties that are not evident from their overt behavior. *Neurology*® 2012;78:816–822

GLOSSARY

CRS-R = Coma Recovery Scale–Revised; **MCS** = minimally conscious state; **TBI** = traumatic brain injury; **VS** = vegetative state.

Patients in the minimally conscious state (MCS) are distinguished from those in the vegetative state (VS) (also referred to as unresponsive wakefulness syndrome[1]) by the presence of inconsistent but reproducible signs of awareness.[2–4] The behavioral assessment of awareness is notoriously challenging in these patients, because responses may be minimal or only inconsistently present. This has led to a misdiagnosis rate of ~40% of VS patients who, in fact, exhibit small but reproducible evidence of awareness when assessed by an experienced clinical team.[5–7]

Functional neuroimaging has established that, even when extensive behavioral assessment concludes that a patient is unaware, it does not necessarily follow that awareness is truly absent.[8–10] In

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Patient	Gender	Age at assessment, y	Interval postictus, mo	Etiology	CRS-R score	No. of trials contributing to analyses	EEG classification accuracy (significant command-following)
1	M	27	48	Anoxia	9	118	58.47[a]
2	M	17	18	Anoxia	10	203	55.67[a]
3	F	48	15	Anoxia	7	120	45.00[a]
4	F	30	9	Anoxia	10	127	55.12[a]
5	M	11	36	Anoxia	13	131	54.20[a]
6	F	58	1	Stroke	8	118	38.98[a]
7	M	43	15	Stroke	10	173	58.38[a]
8	M	79	1	Stroke	10	89	61.80[a]
9	F	37	13	Traumatic	11	174	71.84[b]
10	M	66	21	Traumatic	10	178	56.74[a]
11	F	24	10	Traumatic	12	102	63.73[c]
12	M	46	17	Traumatic	13	125	57.60[a]
13	M	30	3	Traumatic	12	100	45.00[a]
14	M	24	88	Traumatic	13	142	54.23[a]
15	M	36	43	Traumatic	8	201	39.30[a]
16	M	30	109	Traumatic	13	133	45.11[a]
17	M	24	36	Traumatic	16	88	70.45[b]
18	F	59	12	Traumatic	14	165	52.12[a]
19	F	39	12	Traumatic	10	108	63.89[c]
20	M	25	72	Traumatic	15	173	57.23[a]
21	M	52	35	Traumatic	16	167	52.10[a]
22	M	23	66	Traumatic	15	117	63.25[c]
23	M	65	22	Traumatic	7	112	50.00[a]

Abbreviation: CRS-R = Coma Recovery Scale–Revised.
[a] Not significant.
[b] $p < 0.001$.
[c] $p < 0.01$.

one such EEG study, 19% of VS patients were capable of reliably and consistently following commands with their EEG responses, despite being entirely unable to do so behaviorally.[8]

Nontraumatic brain injury (non-TBI) VS patients are known to be less likely than TBI patients to regain an ability to express their awareness overtly[11] and similarly detrimental effects on covert cognition in VS patients have been reported in a number of functional neuroimaging studies.[8,12,13] The effect of etiology on the MCS, however, is poorly understood.[14–16] In this study, we assessed the covert command-following abilities[8] of a group of MCS patients (15 TBI and 8 non-TBI). Based on the relationship between etiology and prognosis already reported in VS groups, we predicted that a greater proportion of TBI MCS patients would be capable of successfully completing this task than non-TBI MCS patients.

METHODS **Patients.** A convenience sample of 25 MCS patients were assessed at 2 European centers, Addenbrooke's Hospital, Cambridge, UK, and University Hospital of Liège, Liège, Belgium. Data from 2 patients were excluded from the analyses because of excessive muscular artifacts in the EEG recordings. Demographic and diagnostic information for the remaining 23 patients are presented in tables 1 and 2. Fifteen of the patients had sustained a TBI, whereas the remaining 8 had sustained a non-TBI.

Ethical approvals and patient consent. Informed assent was acquired from all patients' families and medical teams. For patients tested in Cambridge, ethical approval was provided by the National Research Ethics Service (National Health Service, UK). Ethical approval for those tested in Liège was provided by the ethics committee of the University Hospital and Faculty of Medicine of the University of Liège.

Behavioral assessment. All patients were admitted for 4–5 days as part of a separate protocol and were assessed with the Coma Recovery Scale–Revised (CRS-R)[17] (table 3), an international standard in the assessment of the VS and MCS, daily throughout their admissions. The highest CRS-R score and diagnosis across all assessments are included in table 1.

Table 2	Coma Recovery Scale-Revised subscale scores for each patient[a]					
Patient	Auditory Function	Visual Function	Motor Function	Oromotor/Verbal Function	Communication	Arousal
1	Reproducible Movement to Command	None	Localization to Pain	Reflexive	None	Without Stimulation
2	Reproducible Movement to Command	Startle	Flexion Withdrawal	Vocalization	None	Without Stimulation
3	Localization to Sound	Fixation	None/flaccid	Reflexive	None	Without Stimulation
4	Startle	Pursuit	Flexion Withdrawal	Vocalization	None	Without Stimulation
5	Reproducible Movement to Command	Reaching	Flexion Withdrawal	Vocalization	None	Without Stimulation
6	Startle	Pursuit	Flexion Withdrawal	None	None	Without Stimulation
7	Localization to sound	Pursuit	Abnormal Posturing	Reflexive	None	Attention
8	Reproducible Movement to Command	Startle	Flexion Withdrawal	Verbalization	None	With Stimulation
9	Localization to sound	Pursuit	Flexion Withdrawal	Vocalization	None	Without Stimulation
10	Startle	Pursuit	Localization to Pain	Reflexive	None	Without Stimulation
11	Startle	Pursuit	Localization to Pain	Vocalization	None	Without Stimulation
12	Reproducible Movement to Command	Recognition	Flexion Withdrawal	Reflexive	None	Without Stimulation
13	Reproducible Movement to Command	Reaching	Flexion Withdrawal	Reflexive	None	Without Stimulation
14	Reproducible Movement to Command	Pursuit	Automatic Response	None	None	Without Stimulation
15	Reproducible Movement to Command	None	Flexion Withdrawal	Reflexive	None	Without Stimulation
16	Reproducible Movement to Command	Recognition	Flexion Withdrawal	Reflexive	None	Without Stimulation
17	Reproducible Movement to Command	Recognition	Automatic Response	Reflexive	None	Without Stimulation
18	Reproducible Movement to Command	Recognition	Flexion Withdrawal	Vocalization	None	Without Stimulation
19	Localization to Sound	None	Flexion Withdrawal	Vocalization	Nonfunctional	Attention
20	Reproducible Movement to Command	Reaching	Object Manipulation	Reflexive	None	Attention
21	Reproducible Movement to Command	Reaching	Object Manipulation	Vocalization	None	Attention
22	Reproducible Movement to Command	Reaching	Automatic Response	Reflexive	Nonfunctional	With Stimulation
23	Reproducible Movement to Command	None	Abnormal Posturing	Vocalization	None	With Stimulation

Abbreviation: CRS-R = Coma Recovery Scale–Revised.
[a] See table 3 for a full breakdown of the scale.

Motor imagery task procedure. The EEG task was separated into 2 blocks, right-hand imagery and toe imagery. All patients completed at least 4 blocks of each type of movement (range 4–8), dependent on the patient's level of agitation at the time of assessment. Block order was pseudo-randomized so that no more than 2 blocks of the same imagery type were completed consecutively. Each block began with the auditory presentation of the task instructions for that block. For the right-hand and toe blocks, respectively, the instructions were as follows: "Every time you hear a beep, try to imagine that you are squeezing your right-hand into a fist and then relaxing it//wiggling all toes on both your feet, and then relaxing them. Concentrate on the way your muscles would feel if you were really performing this movement. Try to do this as soon as you hear each beep."

The instructions were followed (after 5 seconds), by the binaural presentation of 15 tones (600 Hz, 60-msec duration) with an interstimulus interval of between 3 and 6.5 seconds (randomly selected from a uniform distribution on each trial). Each block concluded with an instruction to relax. All participants were provided with a short break before the onset of the next block.

EEG preprocessing. EEG was recorded from either a 129-electrode cap (Cambridge, UK) or a 257-electrode cap (Liège; Electrical Geodesics Inc., Eugene, OR) referenced to the vertex. To equalize the number of channels across patients, the 129 channels corresponding to those in the 129-electrode cap were subsequently selected from the 257-channel cap. This step ensured that the same number of EEG features was used for classification of motor imagery and that accuracies were comparable across centers. Data were filtered offline between 1 and 40 Hz, segmented into epochs of 5.5 seconds (including 1.5 seconds before each tone) and baseline corrected within 500 msec before the tone. Bad channels were identified by inspection (channel variance $>\sim$250) and replaced with interpolations of their neighbors (InvDist, EEGLAB[18]). All channels, including the online reference, were rereferenced offline to the average of their 4 geodesically nearest neighbors using a Laplacian operator. Trials containing large movement artifacts were excluded. A median of 127 trials contributed to each patient's single-trial analysis (range 88–203). The 25 electrodes located over the motor area (covering the area centrally from C3 to C4) were selected from the original 129 electrodes to contribute to the single-trial classification, because this is the area of the scalp over which motor imagery–related activity is known to be localized. The median number of channels from these 25 that were interpolated before the analyses was 2 (range 0–10).

Classification analyses. For each patient, a linear support vector machine classifier was trained with the filtered and artifact-rejected data to classify single trials into one of 2 classes (right-hand or toe motor imagery). EEG data from the 25 electrodes selected across the motor cortex in every trial were downsampled to 100 Hz. Log power values within the mu (7–13 Hz),

Table 3 Subscale diagnostic criteria for VS, MCS, and EMCS from the CRS-R[17]

Diagnosis	Scale
Auditory Function Scale	
MCS	4: Consistent Movement to Command
MCS	3: Reproducible Movement to Command
VS	2: Localization to Sound
VS	1: Auditory Startle
VS	0: None
Visual Function Scale	
MCS	5: Object Recognition
MCS	4: Object Localization: Reaching
MCS	3: Visual Pursuit
MCS	2: Fixation
VS	1: Visual Startle
VS	0: None
Motor Function Scale	
EMCS	6: Functional Object Use
MCS	5: Automatic Motor Response
MCS	4: Object Manipulation
MCS	3: Localization to Noxious Stimulation
VS	2: Flexion Withdrawal
VS	1: Abnormal Posturing
VS	0: None/Flaccid
Oromotor/Verbal Function Scale	
MCS	3: Intelligible Verbalization
VS	2: Vocalization/Oral Movement
VS	1: Oral Reflexive Movement
VS	0: None
Communication Scale	
EMCS	2: Functional: Accurate
MCS	1: Non-Functional: Intentional
VS	0: None
Arousal Scale	
VS	3: Attention
VS	2: Eye Opening without Stimulation
VS	1: Eye Opening with Stimulation
VS	0: Unarousable

Abbreviations: CRS-R = Coma Recovery Scale–Revised; EMCS = emergence from minimally conscious state; MCS = minimally conscious state; VS = vegetative state.

low beta (13–19 Hz), middle beta (19–25 Hz), and high beta (25–30 Hz) frequency ranges were calculated at each time point. All the band-power values within the action period between 0.5 and 2.5 seconds after the tone in each trial were then concatenated by channel and used to construct a single feature vector for each trial. This allows the classifier to be trained on discrimina-tive spatiotemporal patterns in the EEG across the 2 types of motor imagery. Block-wise cross-validation was used to determine the classifier's generalization error across the entire dataset. Specifically, the classifier was repeatedly trained and tested, by leaving out 2 blocks at a time (one right-hand and one toe block), training on the remaining blocks, and testing the generated support vector machine therefrom with the excluded blocks. During each repetition, features in the training and test set were z score normalized with the mean and SD of the training set. This block-wise cross-validation procedure, along with the pseudo-randomized block order, ensures that task-irrelevant intrablock and interblock correlations in the EEG cannot significantly account for the classification results.
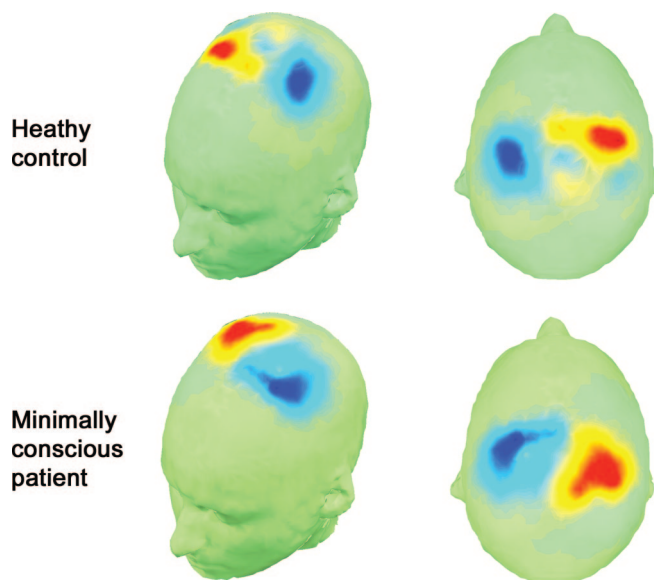
To estimate overall accuracy for a patient, all the binary single-trial classification outcomes from the block-wise cross-validation procedure above were concatenated and modeled as a binomial process (using the binofit function of MATLAB). This procedure assumed that the individual classification outcomes were binomially distributed and calculated the maximum likelihood estimate of the overall correct classification probability. These maximum likelihood estimates were then converted to percent accuracy scores. Finally, a test of whether the 99% and 99.9% confidence intervals for the estimates included chance (50%) was used to ascribe a significance level to each score. All calculations were performed in MATLAB, using a combination of custom scripts and EEGLAB[18] functions.

Group-level statistics. Fisher exact tests (one-tailed) were performed (using SPSS v.19) to compare the proportions of TBI and non-TBI patients who returned positive EEG outcomes. Mann-Whitney tests were used to contrast the CRS-R scores across these patient groups. Correlations with CRS-R score were calculated using the Spearman rho. An α of 0.05 was used for all of these tests.

RESULTS Of all MCS patients, 22% (5 of 23) were able to follow a command in a way that was significantly detectable with this EEG technique (figure) (individual classification accuracies are listed in table 1). The classification accuracies for these 5 patients ranged from 63% to 72% (mean 67%). When separated according to etiology, no non-TBI MCS patients (0 of 8) were capable of successfully following commands with the EEG task, compared with 33% (5 of 15) of TBI MCS patients. This difference across etiology was marginally significant in a Fisher exact test (one-tailed, $p < 0.09$).

To ensure that the difference across etiology was not driven by the significantly lower-level behaviors exhibited by non-TBI patients (as indexed by CRS-R score; see Behavioral assessment), a median split of the TBI MCS patients (median 13) was performed to create a group of low-functioning TBI MCS patients with CRS-R scores comparable to those of their non-TBI peers. The median CRS-R score of both the non-TBI MCS group and the new median-split subgroup of low-functioning TBI MCS patients was 10 and did not differ significantly (Mann-Whitney $U[7,8] = 23$, $p > 0.61$) nor did the 2 groups differ significantly in age or time postictus (all

Heathy control

Minimally conscious patient

The neurophysiologic bases of the positive EEG outcome, with clear foci over the hand and toe motor areas, are formally identical in a comparison between a healthy control participant and one representative minimally conscious state patient who significantly followed commands with this EEG task (patient 22; tables 1 and 2). Maps show the scalp distribution of the single feature, time point × frequency band, with the highest absolute coefficient value from one training run of the cross-validation procedure. Red colors indicate coefficient values greater than zero; blue colors indicate values less than zero. Healthy control data were taken from Cruse et al.[8]

2 independent-samples t tests. The CRS-R scores of non-TBI patients (median 10; range 7–13) were significantly lower than those of TBI patients (median 13, range 7–16; Mann-Whitney U [8,15] = 24.5, $p < 0.05$).

DISCUSSION With use of an EEG motor imagery paradigm, 22% (5 of 23) of a group of MCS patients were able to produce ~100 responses to command without exhibiting any external behavior (figure). When separated according to etiology, a greater proportion of TBI patients returned positive EEG outcomes (33%, 5 of 15) compared with non-TBI patients (0%, 0 of 8). This pattern was also mirrored in the patients' behavioral profiles, with non-TBI patients returning significantly lower scores on behavioral assessments of consciousness (CRS-R score). Crucially, the effect of etiology on the ability to successfully complete this EEG task was statistically robust after these differential behavioral abilities were factored out, indicating that the relatively fewer behavioral markers of consciousness displayed by non-TBI patients are likely to be accurate reflections of their covert cognitive capacities. Conversely, and more remarkably, one-third of the TBI MCS patients possessed a range of high-level cognitive abilities that were not evident from their external behavior, but which were required to complete this EEG task. These include extensive sustained attention, language comprehension, working memory, and response selection, all high-level functions that are commonly associated with normal consciousness (for a full description of these arguments, see Cruse et al.[8]).

As a result of the strains of rapid acceleration and deceleration on the brain, the most common neuropathologic changes after TBI are diffuse axonal injury,[19,20] which predominantly affects both hemispheres, the corpus callosum, brainstem, and cerebellum in the VS and MCS.[21–23] Conversely, when these conditions are caused by a nontraumatic injury, such as hypoxic-ischemic encephalopathy, selective and widespread damage to the neocortex and thalamus is observed, possibly due to the differences in the oxygen requirements of these structures.[24–26] In the broadest sense then, what is known about the neuropathologic mechanisms underlying TBI and non-TBI, particularly in relation to the relative preservation of the cortex after TBI, is reflected here in the differential degree of functional deficit observed across the 2 groups.

The adverse effect of nontraumatic etiology on covert command-following abilities is consistent with that found in other functional neuroimaging studies of covert cognition. None of a group of 22

$p > 0.65$). A Fisher exact test confirmed that, despite the equalization of the median CRS-R score, the proportions of non-TBI patients successfully completing this EEG task were significantly lower than those of their CRS-R score–matched TBI MCS peers (0 of 8 vs 3 of 7; one-tailed, $p < 0.05$).

Three of the 8 MCS patients who were incapable of following commands with their behavior returned positive EEG outcomes (tables 1, 2, and 3). When separated according to etiology, 3 of 4 TBI MCS patients who could not follow commands behaviorally were capable of following commands with this EEG paradigm, compared with none of the non-TBI MCS patients.

Across all MCS patients, classification accuracy was not significantly correlated with CRS-R score (Spearman rho = 0.30, $p > 0.05$), and there were no significant differences in CRS-R scores between those patients successfully completing the EEG task and those not (Mann-Whitney U[5,18] = 62, $p > 0.05$). Two one-way analyses of variance with the factor of EEG outcome (positive/null) revealed no significant differences in the ages or times postictus of the patients in these 2 groups (all $F < 2.2$).

There were no significant differences in the ages of patients and the times postictus when separated according to etiology (traumatic or nontraumatic) in

non-TBI VS and MCS patients were capable of successfully following commands during an fMRI mental imagery task.[10] Indeed, this difference relative to TBI patients (16%, 5 of 32) approached statistical significance (Fisher exact test, one-tailed, $p = 0.058$). An investigation of whether a group of 41 VS and MCS patients could produce appropriate fMRI activations when passively listening to speech, compared with nonspeech, found that significantly more TBI patients showed appropriate activations in this contrast (57%, 15 of 26), compared with non-TBI patients (20%, 3 of 15; Fisher exact test, one-tailed, $p < 0.05$).[13] In an event-related potential study, which required patients to count the occurrences of a target word in a stream of distractor words, a small effect of etiology was reported, with 71% of TBI MCS patients (5 of 7) appearing to follow command, albeit inconsistently, compared with 57% of non-TBI MCS patients (4 of 7).[27] In the assessment of one TBI MCS patient and one non-TBI MCS patient, evidence for covert command-following was reported in the EEG response of the TBI patient only,[28] whereas similar signs of command-following were observed in the fMRI responses of 1 of 3 TBI MCS patients and 1 of 4 non-TBI patients.[29]

The Multi-Society Task Force on Persistent Vegetative State[11] reviewed the outcome of 754 published cases of VS and found that an adult patient who is in a VS within 1 month of a TBI has a 52% chance of recovering consciousness within 1 year, whereas a non-TBI patient has only a 15% chance of doing so. With regard to prognosis from the MCS, however, little is known. In one report, of the 16 TBI MCS patients assessed, 6 regained functional communication at the 5-year follow-up (38%) compared with only 1 of the 7 patients who were in an MCS as a result of anoxic-ischemic injury (14%).[14] Although prognosis for VS and MCS patients was not reported separately, a further study found that 77% of 22 TBI patients had emerged from the MCS at long-term follow-up (1–4 years) compared with only 57% of 14 non-TBI patients and that 77% of TBI patients were capable of interactive communication at that time, whereas only 29% of non-TBI patients were able to do so.[15,16]

Despite the introduction of the MCS diagnostic category almost 10 years ago,[2] to date there have been no large-scale epidemiologic studies of prognosis from this state. As a result, it is not known how often MCS patients recover and to what degree. For example, in one notable case, Terry Wallis was in an MCS for 19 years before emerging to a level at which functional and expressive communication was possible, yet the frequency with which such cases occur has not been systematically investigated.[30] Indeed, in contrast to the VS, a diagnosis of permanent MCS cannot currently be made. Nevertheless, the data reported here suggest that there is a decreased likelihood that non-TBI MCS patients will possess high-level cognitive faculties, whether these may be expressed overtly or not, convergent with the general consensus within the wider literature on this topic. In this context, our results show that etiologic factors produce a clearly measurable difference in remarkably high-level, demanding cognitive functions that subserve awareness, including language, attention, working memory, task orientation, and decision making.

The current data also reemphasize the disparity between behavioral signs of awareness and those that may be detected with functional neuroimaging. Thirty-eight percent of the 8 MCS patients who were incapable of following commands with their behavior, i.e., those producing only low-level nonreflexive behaviors such as visual pursuit, were nevertheless capable of following-command with this EEG paradigm (tables 1, 2, and 3). Indeed, 75% of TBI MCS patients who could not follow commands behaviorally (3 of 4) were capable of returning a positive EEG outcome, compared with none of the non-TBI MCS patients. This result adds to the significant body of evidence that an apparent inability to follow commands with external responses does not necessarily reflect the true absence of the cognitive capability to do so.[8–10,27] Rather, a significant proportion of behaviorally nonresponsive patients retain a range of high-level cognitive capacities beyond those indicated by their behavior.

We have shown that patients who progress to the MCS after a non-TBI are significantly less likely to produce evidence of high-level cognitive functioning than traumatically injured MCS patients. This finding holds true for the conventionally used externally observable signs of cognition, as assessed by behavioral scales (e.g., CRS-R), as well as for covert faculties as determined by the current EEG motor-imagery assessment. Evidence for the differential effect of etiology on the behavior of MCS patients is sparse, and future large-scale epidemiologic studies are required to fully characterize this challenging diagnostic category.[31]

AUTHOR CONTRIBUTIONS

Dr. Cruse: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Chennu: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Chatelle: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Fernández-Espejo: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Bekinschtein: study concept or design, analysis or interpretation of data. Dr. Pickard: drafting/revising the manuscript, study concept or design, study supervision, obtaining funding. Dr. Laureys: drafting/revising the manuscript, study concept or design, study supervision, ob-

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