Voluntary brain processing in disorders of consciousness

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ABSTRACT

Background: Disentangling the vegetative state from the minimally conscious state is often difficult when relying only on behavioral observation. In this study, we explored a new active evoked-related potentials paradigm as an alternative method for the detection of voluntary brain activity.

Methods: The participants were 22 right-handed patients (10 traumatic) diagnosed as being in a vegetative state (VS) (n = 8) or in a minimally conscious state (MCS) (n = 14). They were presented sequences of names containing the patient's own name or other names, in both passive and active conditions. In the active condition, the patients were instructed to count her or his own name or to count another target name.

Results: Like controls, MCS patients presented a larger P3 to the patient's own name, in the passive and in the active conditions. Moreover, the P3 to target stimuli was higher in the active than in the passive condition, suggesting voluntary compliance to task instructions like controls. These responses were even observed in patients with low behavioral responses (e.g., visual fixation and pursuit). In contrast, no P3 differences between passive and active conditions were observed for VS patients.

Conclusions: The present results suggest that active evoked-related potentials paradigms may permit detection of voluntary brain function in patients with severe brain damage who present with a disorder of consciousness, even when the patient may present with very limited to questionably any signs of awareness. *Neurology*® 2008;71:1614–1620

GLOSSARY

CRS-R = Coma Recovery Scale-Revised; **EOG** = electro-oculogram; **ERP** = evoked-related potentials; **MCS** = minimally conscious state; **SON** = subject's own name; **UN** = unfamiliar first names; **VS** = vegetative state.

Behavioral assessment is currently one of the main methods used to detect signs of awareness in severely brain injured patients recovering from coma.[1] However, disentangling the vegetative state from the minimally conscious state is often difficult when relying only on behavioral observation.[2] Whereas the vegetative state (VS)[3] is characterized by preserved autonomous functioning (e.g., preserved sleep-wake cycles) without awareness of oneself or of the environment, patients in the minimally conscious state (MCS)[4] present reproducible signs of awareness such as purposeful eye movements or response to verbal order. However, these behaviors are often fluctuating and their detection can be unreliable. The rate of misdiagnosis is quite high, as recent studies have observed that 37% to 43% of patients diagnosed as being in a VS actually show signs of awareness.[5-7] This high rate of misdiagnosis can be explained by several factors such as arousal fluctuation, motor disabilities, poor expertise in behavioral assessment, or the use of insensitive behavioral assessent scales. As misdiagnosis has consequences on treatment and end-of-life decisions,[8]

Supplemental data at www.neurology.org

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Table 1 Demographic and evoked-related potentials data in patients in a vegetative state (VS)

Patient	Age, y	Gender	Etiology	Time since onset	SON (P3)	Active SON (P3)	Active TUN (P3)
VS 1	79	M	Trauma	12 d	–	–	–
VS 2	49	M	Anoxia	2.6 y	–	–	–
VS 3	53	M	Stroke	2 mo	–	–	–
VS 4	36	F	Anoxia	2.6 y	–	–	–
VS 5	25	M	Trauma	1.7 mo	–	–	–
VS 6	42	F	Anoxia	5.8 mo	–	–	–
VS 7	36	M	Trauma	7.6 y	–	–	–
VS 8	55	M	Encephalitis	1.8 mo	–	–	–

SON = subject's own name; active SON = counting own name; active TUN = counting target unfamiliar name.

developing additional methods in order to improve the detection of signs of consciousness is therefore crucial.

Cognitive evoked-related potentials (ERP) assess electrical brain responses to stimulations across time and can be performed at the patient's bedside. Recently, we elaborated a passive ERP paradigm in which participants passively listened to their own first name and to unfamiliar first names. A P3 component was observed in response to the participant's name in all healthy volunteers, in all MCS patients, and also in 3 out of 5 VS patients.[9] This suggested that automatic processes for speech are preserved in a great number of patients in altered states of consciousness. The use of a passive ERP paradigm is nevertheless not sufficient to reliably disentangle VS from MCS patients. Indeed, even if passive ERP paradigms are able to highlight ongoing brain processing for a given stimulus input, they do not differentiate between voluntary and automatic cognitive processes and, therefore, between conscious and unconscious brain processing. For this reason we developed a new active ERP paradigm where the participant is instructed to voluntarily direct attention to a target stimulus and to ignore other stimuli. The present study validates this paradigm for application in severely brain injured patients with altered states of consciousness.

METHODS

Participants. This study was conducted in 29 severely brain injured patients recovering from coma. Inclusion criteria were 1) no centrally acting drugs, 2) no neuromuscular function blockers and no sedation within the prior 24 hours, 3) periods of eye opening (indicating preserved sleep-wake cycles), and 4) a diagnosis of VS or MCS, established according to internationally established criteria.[3,4]

Twenty-two right-handed patients (49 ± 15 years; 15 men) were retained for the analyses reported here (the data of 7 patients had to be discarded due to technical problems or low quality recordings with respect to ocular, muscle, or noise artifacts). The etiology of brain injury was traumatic (n = 10), postanoxic (n = 8), stroke (n = 1), hemorrhagic (n = 1), metabolic (n = 1), or encephalitis (n = 1). Eighteen patients were in a chronic stage (from 1.1 months to 23.7 years post-insult) and 4 in the acute stage (from 12 to 22 days post-insult). Eight patients were diagnosed as being in a VS (47 ± 16 years; 3 traumatic; 7 chronic patients) and 14 in MCS (50 ± 15 years; 7 traumatic; 11 chronic patients) (tables 1 and 2 and table e-1 on the *Neurology*® Web site at www.neurology.org). All patients were right-handed as assessed by heteroanamnesis. None had a history of impaired auditory acuity. Twelve age-matched right-handed healthy volunteers (8 men; 53 ± 9 years) also participated in the experiment. The person's first language was French for all the patients and the matched controls. The study was approved by the ethics committee of the Medical Faculty of the University of Liege and written informed consent was obtained by the patient's family.

ERP paradigm. Nine sequences of 120 auditory stimuli were developed. Each sequence included 8 first names (the subject's own name [SON] and 7 other unfamiliar first names [UN]) repeated 15 times and presented in a randomized order. The UN were selected from previous studies[9,10] and were all of high frequency of use in the French language. The interstimulus interval time was 1,500 msec. Each patient's family was asked whether some of the unfamiliar names had an emotional importance for the patient (e.g., close relative's name). The emotionally significant names were excluded from the analysis. All stimuli had been recorded by the same female voice with a neutral intonation, digitized, and then replayed binaurally during the experiment (at maximum 90 dB sound pressure level).

The ERP paradigm included one passive and two active conditions (three sequences per condition). The passive listening condition was first presented to the subject. Then, two active conditions presented in randomized order followed. In the active conditions, the patient was asked to either count one specified target unfamiliar name (TUN active condition), or to count her or his own first name (SON active condition).

ERP acquisition. Stimuli were presented via earphones and data were acquired at the bedside. ERP recordings were performed with the subjects' eyes open (i.e., patient being awake) and minimal ambient noise. EEG activity was recorded from three central electrodes (Fz, Cz, and Pz)[11] and referenced to the nose. Electro-oculogram (EOG) was acquired using two electrodes placed diagonally above and below the right eye; the electromyogram (EMG) was recorded using two electrodes placed on the chin. A ground electrode was placed near Fz and impedances were kept below 5 kΩ. EEG acquisition was performed with a sampling rate of 500 Hz by means of a NuAmp EEG amplifier (NeuroSoft, Sterling, VA) with analog bandpass filtering of 0.1–200 Hz. The patient was briefly stimulated (i.e., deep pressure stimulation or auditory stimuli)[12] just before each sequence in order to ensure sufficient arousal level. A 5-minute break separated each condition of the ERP paradigm.

ERP analyses. Using Neuroscan software (NeuroSoft), single epochs (−200 to 1,300 msec) with an amplitude $\geq \pm 75$ μV on EOG electrodes or with electromyographic artifacts

Table 2 Demographic and evoked-related potentials data in patients in a minimally conscious state (MCS)

Patient	Age, y	Gender	Etiology	Time since onset	SON (P3)	Active SON (P3)	Active TUN (P3)
MCS 1	35	M	Trauma	23.7 y	+	+	−
MCS 2	47	F	Hemorrhage	7.2 mo	+	−	−
MCS 3	26	M	Trauma	4.3 y	+	+	−
MCS 4	63	F	Trauma	3.6 mo	+	+	−
MCS 5	56	M	Anoxia	1.1 mo	+	−	+
MCS 6	26	M	Anoxia	3.1 y	+	−	−
MCS 7	59	M	Trauma	8.8 mo	+	−	+
MCS 8	50	F	Anoxia	1.9 mo	+	−	−
MCS 9	36	F	Trauma	22.3 y	+	−	−
MCS 10	55	M	Anoxia	22 d	+	+	−
MCS 11	54	M	Trauma	22 d	+	+	−
MCS 12	50	F	Anoxia	6.9 y	+	−	+
MCS 13	70	M	Metabolic	16 d	+	−	+
MCS 14	74	M	Trauma	1.1 mo	+	−	−

SON = subject's own name; active SON = counting own name; active TUN = counting target unfamiliar name.

were discarded from further analysis. ERP were averaged as a function of target (i.e., SON or TUN) and non-target (i.e., average of the six not-to-be-counted UN) events in each condition. In order to ensure equivalent signal-to-noise ratios, we compared ERP to targets and non-targets obtained with a same number of trials (the non-target stimuli preceding the targets were selected). The averaged data were digitally filtered from 1 to 40 Hz (roll off: 6 db/oct). Grand-averaged ERP were constructed for all control subjects and for all VS and MCS patients.

Statistical analysis. Amplitudes and latencies of the N1, P2, N2, and P3 components were calculated for individual averages. For each component, we chose the maximum amplitude and its associated latency (in a temporal window predefined on grand-averaged ERP). Amplitude and latency values were tested with mixed repeated measures analyses of variance on component (N1 vs P2 vs N2 vs P3), stimulus (target: SON in passive and in SON active conditions or TUN in TUN active condition vs non-target: not-to-be-counted UN in each condition), and electrode position (Fz vs Cz vs Pz) as within-subject factors, and group as between-subject factor (control vs VS vs MCS). Significant interactions were further explored using Tukey post hoc analyses. Individual analyses were conducted when significant post hoc differences were observed: amplitude differences between targets and non-targets in each of the three conditions and between targets in passive and targets in active conditions were tested at an individual level at Fz, Cz, and Pz using t scores. This analysis takes into account the variance of the EEG recordings composing the averaged ERP.[9] t Scores were computed for each participant in a temporal window of 50 msec around the peak latency of each component. Results were considered significant when p values were below 0.05 within the temporal window of 50 msec.

Behavioral assessment. The Coma Recovery Scale-Revised (CRS-R)[12] was administered after the ERP measurements in order to avoid fatigue during the ERP recordings (table e-1). The CRS-R has been designed to differentiate VS from MCS[7] and consists of 23 hierarchically arranged items that comprise six subscales addressing arousal, auditory, visual, motor, oromotor/verbal, and communication functions. The lowest item on each subscale represents reflexive activity while the highest item represents cognitively mediated behaviors. A second behavioral assessment was performed during the week following the ERP recordings session in order to increase diagnosis reliability.

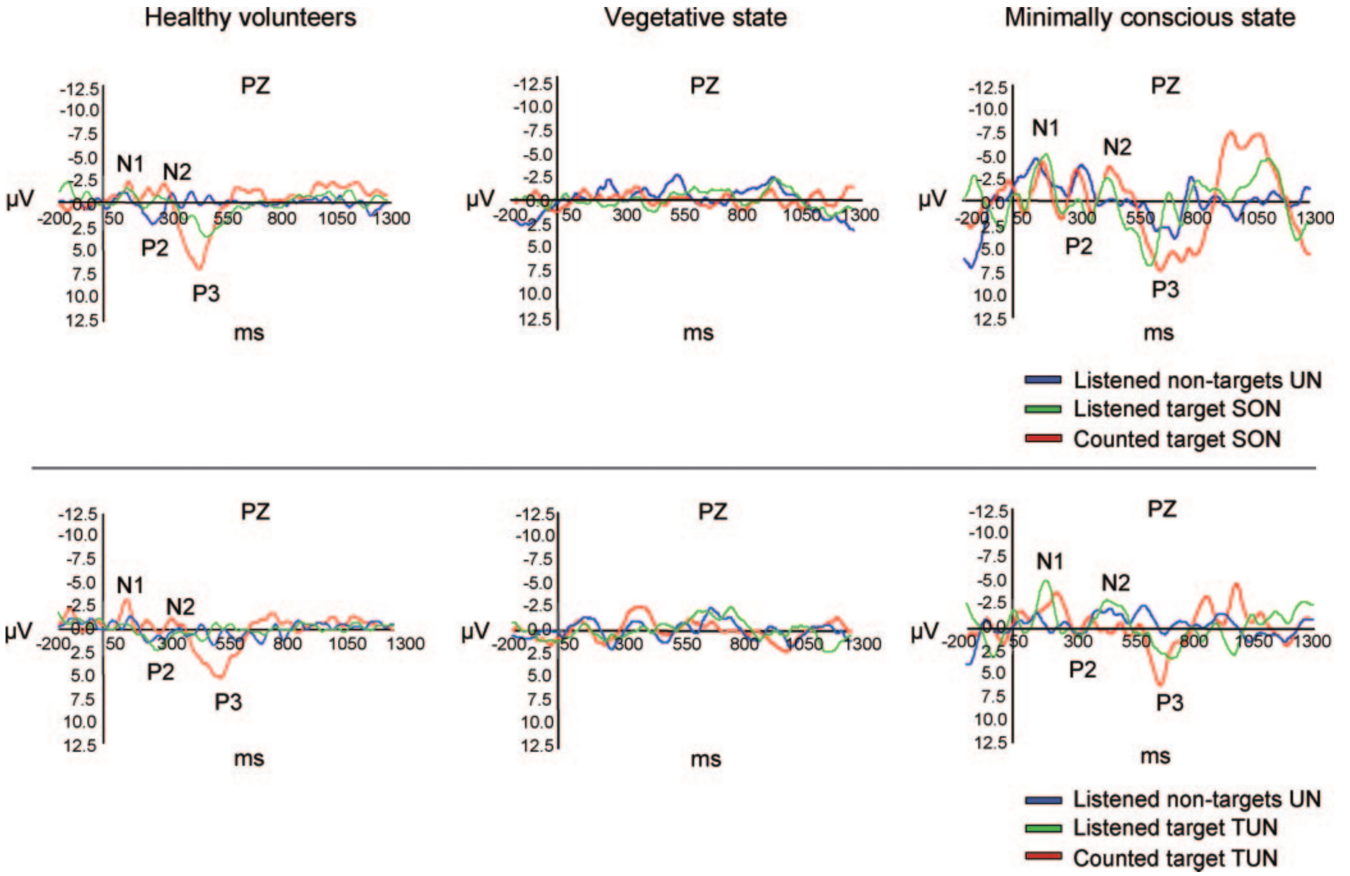
RESULTS Analyses of variance showed no main group effect ($F = 0.58$; $p = 0.56$) on ERP amplitudes (among controls, VS, and MCS patients). However, the analysis demonstrated a strong interaction effect among group, component, and target ($F = 40.6$; $p < 0.01$). Post hoc analyses did not show any significant amplitude difference between stimuli (i.e., target vs non-target) for N1, P2, and N2 components, in either the control or the patient groups (VS and MCS). Differences between stimuli were only observed for the P3 wave in the control and MCS groups (see figure and details below). No differences were obtained for each of these components (including the P3 component) in the VS group (see figure and tables 1 and 3).

In controls, a larger P3 response was observed for the listened SON vs the listened UN in the passive condition ($F = 18.54$; $p < 0.001$). Moreover, a significantly higher P3 was obtained when the targets SON and TUN were counted (in the active conditions) rather than only listened (in the passive condition). A larger P3 was also observed, in the two active conditions, for the counted targets SON and TUN as compared to non-counted targets (UN) (see table 3). The results were identical when considering each control subject individually.

For the MCS group, a larger P3 response was observed for the listened SON vs the listened UN in the passive condition ($F = 7.97$; $p = 0.01$). This was observed in all MCS patients. Moreover, a significantly higher P3 was obtained when the target TUN had to be counted (in the active condition) rather than only listened (in the passive condition). A larger P3 was also observed in the two active conditions for the counted targets SON and TUN as compared to non-counted targets (UN) (see table 3). The amplitude of these P3 responses was not significantly different from controls. More exactly, at an individual level, 9 out of 14 patients showed larger P3 amplitude when the target TUN ($n = 4$) or the target SON ($n = 5$) had to be counted (in the active conditions) as compared to the condition where these targets had only to be listened (in the passive condition) and as compared to non-counted targets (UN) (see table 2).

P3 amplitude was therefore higher in 9 out of 14 MCS patients for the counted target in one out of

Figure Grand-averaged evoked-related potentials in healthy volunteers (n = 12), vegetative patients (n = 8), and minimally conscious patients (n = 14) at Pz



Upper panels depict the response to the subject's own name (SON) in the passive condition (listened target SON; in green) and in the active condition (counted target SON; in red) vs unfamiliar names (listened non-targets UN; in blue). Lower panels depict the response to the target unfamiliar name (TUN) in the passive condition (listened target TUN; in green) and in the active condition (counted target TUN; in red) vs unfamiliar names (listened non-targets UN; in blue).

the two active conditions. Using χ^2 analyses, we tested whether the proportion of patients who responded was different as a function of the task (i.e., counting SON vs TUN) or the order of presentation (i.e., performing the first vs the second task presented). We observed a significant difference according to the order of presentation ($\chi^2 = 4.5$; $p = 0.05$) but not according to the task ($\chi^2 = 0.45$; $p > 0.05$).

As regards to latencies, analysis of variance showed a significant interaction between group and

Table 3 Evoked-related potentials amplitudes (in μV) for P3 component in response to targets in both passive (listened SON and TUN) and active (counted SON and TUN) conditions for controls, vegetative (VS), and minimally conscious (MCS) patients

	Listened SON	Counted SON	Counted vs listened SON (F values)	Counted SON vs UN (F values)
VS	3.1 ± 4.3	3.7 ± 2.5	0.01	0.10
MCS	8.4 ± 4.7	8.4 ± 6.7	0.84	9.30*
Control	8.9 ± 4.5	12.1 ± 4.6	5.97*	25.52†
	Listened TUN	**Counted TUN**	**Counted vs l istened TUN (F values)**	**Counted TUN vs UN (F values)**
VS	2.7 ± 5.1	2.7 ± 3.6	0.01	0.37
MCS	4.6 ± 3.1	8.1 ± 5.5	4.15*	6.94*
Control	4.3 ± 2.6	10.4 ± 4.4	18.74†	20.26†

F values indicate differences in P3 amplitudes obtained for the counted vs the listened target (SON and TUN) and the counted target (SON and TUN) vs non-counted unfamiliar names (UN).

*$p < 0.05$; †$p < 0.001$.

SON = subject's own name; TUN = target unfamiliar name.

Table 4 **Evoked-related potentials latencies (in ms) for P3 component in response to targets in both passive (listened SON and TUN) and active (counted SON and TUN) conditions for controls, vegetative (VS), and minimally conscious (MCS) patients**

	Listened SON	Counted SON	Counted vs listened SON (F values)	Counted SON vs UN (F values)
VS	454 ± 43	467 ± 58	0.01	0.01
MCS	594 ± 178	653 ± 122	3.88	0.60
Control	457 ± 64	423 ± 46	0.47	1.13
	Listened TUN	**Counted TUN**	**Counted vs listened TUN (F values)**	**Counted TUN vs UN (F values)**
VS	449 ± 58	492 ± 43	1.24	0.22
MCS	659 ± 62	650 ± 109	0.07	0.23
Control	431 ± 54	485 ± 64	3.74	2.16

F values indicate differences in P3 latencies obtained for the counted vs the listened target (SON and TUN) and the counted target (SON and TUN) vs non-counted unfamiliar names (UN).
SON = subject's own name; TUN = target unfamiliar name; UN = unfamiliar names.

component (F = 125.21; $p < 0.001$). We did not observe any significant latency difference between stimuli (i.e., target vs non-target) for N1, P2, N2, and P3 components, in either the control or the patient groups (VS and MCS). However, post hoc analyses revealed that the P3 latency was significantly delayed in MCS as compared to controls for the listened SON (F = 9.80; $p < 0.01$) and TUN (F = 123.89; $p < 0.001$) in the passive condition and for the counted targets SON (F = 50.78; $p < 0.001$) and TUN (F = 31.26; $p < 0.001$) in the active conditions. No significant results were observed for any other component (i.e., N1, P2 or N2) (table 4).

DISCUSSION In all healthy controls and MCS patients, we found a larger P3 response following the presentation of the patient's own name in the passive condition. This replicates previous findings showing that MCS patients have preserved automatic speech processing. Indeed, Perrin and coworkers obtained a larger amplitude in response to the patients' own name as compared to unfamiliar names in all MCS patients. However, three out of five vegetative patients also showed a larger P3 response for their own name.[9] It is known that speech processing can be observed in unconscious state such as anesthesia, for instance. Therefore, passive listening is not sufficient to detect voluntary and therefore conscious brain activity.[13]

Using our active ERP paradigm, we observed in MCS patients a larger P3 response in at least one active condition. We observed this result for the group but also individually. Indeed, the individual analyses revealed that nine MCS patients had a larger P3 response for the counted targets as compared to the not-to-be counted names and as compared to passive listening. Additionally, the P3 amplitude observed in MCS was otherwise equivalent to that observed in controls. This suggests that, like controls, the patients were able to voluntary focalize their attention on the target as a function of task requirements. We nevertheless observed a larger latency for the counted targets in MCS as compared to controls. This possibly reflects reduced speed processing. Indeed, in presence of brain lesions, it is not astonishing to observe more difficulties performing a task in patients as compared to healthy controls.[9]

Importantly, a task-related P3 response was observed in three MCS patients who, at the behavioral level, showed solely visual fixation or pursuit (without response to verbal command on repeated behavioral testing) (table e-1). These results can be related to those observed in an fMRI study using active event-related paradigm. Owen et al., instructing participants to perform mental imagery, showed that brain activation patterns similar to controls were observed in one patient diagnosed with VS but showing visual fixation (not more than 5 seconds), suggesting that this patient was actually able to voluntarily follow task instructions, and hence conscious to some extent.[14] Our patients had to present visual fixation for more than 2 seconds to consider this sign as present (as defined by the CRS-R).[12] According to the Aspen workgroup criteria, visual fixation is considered as a clinical sign defining MCS. The Royal College of Physicians guidelines, however, regard visual fixation and tracking as features that should prompt careful reassessment of the diagnosis of the VS but that do not in themselves negate the diagnosis and therefore would not represent a sign of consciousness.[15] Our ERP study, as well as the fMRI study by Owen et al., suggests that at least some patients showing solely visual fixation or tracking are capable of following commands, and consequently are not vegetative.

The P3 response observed in nine of our MCS patients was obtained in only one of the two active conditions (i.e., counting SON or TUN). Fatigue effects are a likely partial explanatory factor of this observation. The number of patients who solely responded to the first active condition (n = 6) was higher than the number of patients who solely responded to the second active condition (n = 3). This effect is to be expected as MCS is characterized by easily exhausted behavioral responses.[4] We nevertheless cannot exclude the presence of fluctuations in vigilance as three patients only responded to the second active condition. However, the fundamental finding here is that most of the MCS patients (9 out of 14) were able to respond as a function of task requirements in at least one of the conditions, suggesting that they are able to voluntarily follow relatively complex task demands, even if only inconsistently so.

Passive P3 responses to their own name were not observed in our VS patients, although such findings had been previously reported.[9] We also observed no task-related P3 changes in patients diagnosed as being in a VS. This is in line with international diagnostic criteria of VS,[3] considering this state as reflecting reflexive activity but not consciousness. However, negative findings do not necessarily prove absence of consciousness. We should note that no task-related P3 response was observed in 5 out of our 14 MCS patients. As an ERP response was observed in MCS patients showing solely visual fixation or pursuit at the behavioral level, there is no reason that other MCS patients, showing more complex signs of voluntary behavior (e.g., behavioral response to command), would not be able to do this task. False negatives might in part be due to the fact that only one ERP measurement was obtained here for each condition. Multiple ERP assessments (performed on the same day or on different days) would decrease such possibly false negative findings.

The heterogeneity in the etiology and in the neuropathology of the studied population should be mentioned but does not limit the interpretation of our results given the behavioral parameters used to define the patient population studied.

Further studies are needed to better characterize the cognitive components preserved in MCS patients. The employed ERP paradigm implies various functions such as sustained vigilance, selective attention (focused on the "to-be-counted" target), inhibition (of non-targets), and working memory (counting). The larger P3 response obtained for the target name in the active conditions does not necessarily mean that all these cognitive components were successfully used by the MCS patients. Other paradigms will need to be developed in order to assess each of these cognitive components. In clinical practice, this will permit better adaptation of cognitive therapy in these challenging patients. Secondly, the proposed paradigm could and should next be employed as a communicative means for patients clinically considered as minimally conscious.[16]

Until now, few studies have investigated the interest of active paradigms in severely brain damaged patients. Most previous ERP[9,17] and functional neuroimaging[18-21] studies have employed passive paradigms. These studies have shown more widespread and integrated brain activation in MCS as compared to VS patients. However, no previous ERP study employed active paradigms (i.e., patients being asked to actively perform a task) in MCS. Our data lead us to believe that such paradigms allow the exploration of residual cognitive functioning in these patients in a more reliable and valid manner. Most importantly, our results suggest that we most likely underestimate the cognitive capacities of MCS patients and encourage further investigation in this field.[22,23]

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