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Infraclinical detection of voluntary attention in coma and post-coma patients using electrophysiology

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Abstract

Objectives

Early functional evaluation and prognosis of patients with disorders of consciousness is a major challenge that clinical assessments alone cannot solve. Objective measures of brain activity could help resolve this uncertainty. We used electroencephalogram at bedside to detect voluntary attention with a paradigm previously validated in healthy subjects.

Methods

Using auditory-oddball sequences, our approach rests on detecting known attentional modulations of Event Related Potentials that reflect compliance with verbal instructions. Sixty-eight unresponsive patients were tested in their first year after coma onset (37 coma and 31 first year post-coma patients). Their evolution 6 months after the test was considered.

Results

Fourteen of the 68 patients, showed a positive response. Nine were in a coma and 5 in a minimally conscious state (MCS). Except for one who died early, all responders evolved to exit-MCS within 6 months (93%), while 35 (65%) among non-responders only.

Conclusions

Among those patients for whom the outcome is highly uncertain, 21% responded positively to this simple but cognitively demanding test. Strikingly, some coma patients were among responders.

Significance

The proposed paradigm revealed cognitive-motor dissociation in some coma patients. This ability to sustain attention on demand predicted awakening within 6 months and represents an immediately useful information for relatives and caregivers.

Keywords: Coma; consciousness disorders; outcome; electroencephalography; event related potentials; active paradigm

Highlights

- Early detection of voluntary attention in DoC patients is feasible at bedside using EEG.
- In coma a positive response reveals voluntary attention processes and is associated with a high rate of awakening within 6 months.
- In post-coma patients, response to the test proves coherent with the clinical evaluation.

Abbreviations:

MCS: Minimally Conscious State

e-MCS: exit-MCS

DoC: Disorder of Consciousness

EEG: Electroencephalogram

fMRI: functional Magnetic Resonance Imagery

ICU: Intensive Care Unit

VS: Vegetative State

CRS-R: Coma Recovery Scale Revised

GOS-E: Glasgow Outcome Scale Extended

SEPs: Somatosensory Evoked Potentials

AEPs: auditory Evoked Potentials

MMN: Mismatch Negativity

ERPs: Event Related Potentials

GCS: Glasgow Coma Scale

EOG: Electro-oculogram

1. Introduction

Faced with a person with disorder of consciousness (DoC) after brain injury, the most natural questions that immediately arise are: does he/she perceive anything? Will he/she wake up? These questions directly speak to decisions regarding the withdrawal of life-sustaining therapies. However, answering them remains very challenging.

The last decade has seen a huge change in the way we view these patients. We owe this change to several neuroimaging studies using fMRI, to a lesser extend EEG, which enabled some of these patients to provide an overt and reproducible answer to verbal instructions (Bardin et al., 2011; Bekinschtein et al., 2009; Cruse et al., 2012; Monti et al., 2010; Owen et al., 2006; Perrin et al., 2006). Nearly 20% of chronic unresponsive patients proved able to produce specific and reliable patterns of neural activity, on demand. This opened a new era of research, urging the community to assess the acute phase of brain injury, when prognosis is most uncertain, and to rather use EEG given fMRI's lack of portability and high cost (Owen, 2019).

A recent study used EEG in the ICU, and found a dissociation between the absence of behavioral response to motor commands and the evidence of brain activation in EEG responses to these commands, in 15% of the patients (Claassen et al., 2019). Interestingly, this study showed a difference in functional outcomes at 12 months between patients with and without cognitive–motor dissociation.

Beyond the need to replicate those findings, one key question that remains unresolved pertains to actual and future level of awareness of these patients and their ability to communicate.

In the current study, we used EEG at bedside to assess covert cognition in different groups defined on a clinical basis: coma patients who, by definition, are believed to be fully unconscious, but also patients showing post-coma disorders of consciousness either in a Vegetative State (VS) or in a Minimally Conscious State (MCS), the latter being the more likely to provide some brain response to any verbal command. We employed an original task-based

auditory oddball paradigm that, in healthy subjects, proved to be highly sensitive, at the individual level, to reveal voluntary sustained attention in response to specific instructions (Morlet et al., 2017). Importantly, we also assessed the prognostic value of this active EEG test in terms of awakening that we defined as the exit MCS (e-MCS) stage of the coma recovery scale revised (CRS-R) and functional outcome (using the Glasgow Outcome Scale-Extended (GOS-E) level 3 or higher), 6 months after testing.

According to the known definitions of the various post-coma clinical states, we did not expect to find responders to this active test among either VS or MCS- patients. In contrast, we expected that some MCS+ patients would possibly show a significant positive answer. In coma patients, the aim was to openly investigate whether any patient could reveal a strong cognitive-motor dissociation[1] by positively answering to this test.

We specifically addressed the following questions:

1 – Do DoC patients respond to this active test in a manner consistent with their clinical diagnosis at the time of recording?

Since a positive response to the active test requires a voluntary and sustained response to a verbal command, we expected Coma but also VS and MCS- patients to be non-responders, while some MCS+ patients might respond positively.

2 – What is the prognostic value of this test for both responders and non-responders?

For the active test to be valuable in terms of prognosis, it needs to show predictive value, at least for responders or non-responders. In particular, we would expect a valuable positive test to predict awakening (e-MCS) or a functional improvement (GOS-E greater than 2).

[1] Cognitive-Motor Dissociation (CMD) refers to "*... the sharp dissociation of a retained but unrecognized (covert) cognitive capacity in some severely brain-injured patients with non-purposeful or absent behavioral responses*" as initially defined in (Schiff, 2015), and recently discussed in (Schnakers et al., 2022).

2. Methods

2.1 Patients

In the Lyon Neurological Hospital (France), a neurophysiological assessment is typically requested for intensive care patients with delayed awakening, or for patients discharged from intensive care but with DoC status difficult to determine clinically. This assessment always begins with an EEG, and the recording of somatosensory evoked potentials (SEPs), brainstem and middle latency auditory evoked potentials (AEPs). In case of preservation of at least one sensory cortical response type, this evaluation is completed by passive mismatch negativity (MMN) to deviant auditory stimuli and Novelty P3 to the own name (Fischer et al., 2008).

In 2009, we added an active EEG test to these passive event-related potentials (ERPs). In between 2009 and 2015, we recorded 84 patients. We excluded 3 patients due to technical issues during data recording, and 4 others whose clinical course at 6 months was unknown. Of the remaining 77 patients, we focus on the 68 who were tested within one year of coma onset (see supplemental Figure S1).

Among the 68 included patients, 37 had not opened their eyes from coma onset (coma patients) and 31 could open their eyes but had not recovered full consciousness (post-coma DoC). The latter were classified as in a vegetative state (VS) or a minimally conscious state lower (MCS-) or upper (MCS+), as shown in Table 1.

All patients were recorded after a 48 hours sedative treatment break (see Supplemental Digital Content for full details).

This retrospective study, entitled "Contribution to the wakefulness prognosis of an active EEG test detecting sustained attention abilities in coma patients or chronic patients with disorder of consciousness (DoC)" was approved by the ethics committee of the Lyon University Hospital on 22/01/2020 (IRB N°20-08) and is in accordance with the 1975 Declaration of Helsinki.

Since based on anonymized clinical and neurophysiological data collected during coma and post-coma disorders of consciousness, informed consent was waived by our institutional review board.

2.2 *Clinical Assessment*

Clinical evaluation at the time of the test and clinical outcome at 6 months were assessed by a clinician that did not participate to the ERP data analysis.

At the time of the test, the Glasgow Coma Scale (GCS) was assessed in coma patients. In post-coma patients, the Coma Recovery Scale Revised (CRS-R) was assessed.

The clinical outcome was assessed six months after recording using the CRS-R and the Glasgow Outcome Scale Extended (GOS-E), described in supplemental materials. When a patient awoke and then died from independent reason within 6 months, the score obtained at awakening was retained.

2.3 Data acquisition

Auditory stimuli were delivered binaurally through inserted earphones at an intensity of 65 dB HL using Presentation software (Neurobehavioral Systems). A classic auditory two-tone oddball paradigm with frequency deviants was presented in 3 consecutive attention conditions: passive, diverted and focused attention. The instructions in conditions 2 and 3 of the active paradigm were included in the stimulation protocol and delivered binaurally through earphones. Potentials were recorded continuously from seven scalp electrodes (Fz, Cz, Pz, F3, F4 and the two mastoids). The reference electrode was placed on the tip of the nose and the ground electrode on the forehead. One bipolar EOG derivation was recorded from 2 electrodes placed on the supra-orbital and infra-orbital ridges of the right eye. This minimal set of electrodes was

selected for bedside recordings, considering topography of the responses observed with 32 scalp electrodes in healthy subjects.

Electrode impedance was kept below 5 kΩ. The signal was amplified (band-pass 0.3–100 Hz), digitized (sampling frequency 1024 Hz) and stored for off-line analysis, using a Micromed System98 EEG recording system.

2.4 Data analysis

The active auditory paradigm was previously validated in 20 healthy subjects (Morlet et al., 2017). Figure 1 depicts the protocol and the results obtained at the group level in this control population. Two main effects of attention manipulation could be detected: *1) an effect of counting* (COUNT effect) observed in the difference between responses to deviants and standards in the focused attention condition (a centro-parietal COUNT P3 wave, possibly preceded by a fronto-central COUNT N2 wave); *2) an effect of attention manipulation* (FOCvsDIV effect) assessed as the difference between responses to deviants in the focused attention condition and deviants in the diverted attention condition (a centro-parietal FOCvsDIV P3 effect, possibly preceded by a fronto-central FOCvsDIV N2 effect).

ERP components and attention effects were detected individually in each patient using a two-step process. In a first step, objective detection based on point-by-point randomization tests (described below) was performed. In the second step, when the effect of attention was statistically significant, a trained neurologist validated the wave using visual waveform analysis.

2.4.1 ERP pre-processing and averaging:

ERPs were analyzed off-line using the software package for electrophysiology data analysis (ELAN) developed at the DYCOG team of the Lyon Neuroscience Research Center (Aguera et al., 2011), and the scientific programming tool Matlab (The MathWorks, Inc., Natick, MA).

A 30-Hz low-pass digital filter (bidirectional Butterworth, 6th order) was applied to the raw data. In each of the 3 conditions we averaged the responses to standards (except those following a deviant) and to deviants for an epoch of 1700 ms including a prestimulus period of 200 ms. Epochs showing peak-to-peak deflections larger than ±100 μV at any scalp electrode were rejected. When rejection rate was larger than 20%, we considered blink rejection followed by new averaging. Blink correction was carried out in epochs showing peak-to-peak deflections of the EOG larger than 125 μV or absolute value of the first derivative of the EOG exceeding 20 μV/ms. For the trials concerned, blink correction of the raw EEG signal used regression with EOG signals following the method proposed by Gratton et al. (Gratton et al., 1983). In final averaging after blink correction, rejection thresholds could be increased in some patients for exceptionally noisy electrodes, with the objective of a maximum rejection rate of 20%.

The ERPs were eventually baseline-corrected by subtracting the mean value of the signal during the 100 ms prior to stimulus onset.

2.4.2 Objective detection of waves and attention effects

Objective detection of waves (COUNT N2 and P3) and attention effects (FOCvsDIV N2 and P3) was performed on the set of accepted baseline-corrected trials, in spatial and temporal windows derived from previous knowledge. The P300 effect of counting (COUNT P3) between the responses to deviants and standards in the focused attention condition and the P300 effect of attention manipulation (FOCvsDIV P3) between the responses to deviants in the focused and in the diverted conditions were detected in the average of Cz and Pz derivations between 250 and 800 ms. The N2 effect of counting (COUNT N2) between the responses to deviants and standards in the focused attention condition and the N2 effect of attention manipulation

(FOCvsDIV N2) between the responses to deviants in the focused and in the diverted conditions were detected in the average of Fz and Cz derivations between 100 and 500 ms.

We used permutation tests: at each sampling point, the probability that the 2 conditions are different was estimated from 2000 permutations of samples from the 2 conditions. Like in our previous study in healthy subjects, an effect was detected when at least 20 consecutive points showed a significant difference (unilateral permutation $p < .05$). This threshold was extrapolated from the recommendations given by (Guthrie and Buchwald, 1991).

In our previous study (Morlet et al., 2017), a FOCvsDIV effect was observed in 19 of the 20 aware healthy subjects. It turned out that the only subject showing no FOCvsDIV effect was clearly not sufficiently engaged in the task. He was, however, conscious and showed a significant COUNT effect under the condition of focused attention. Considering this result and the fact that a FOCvsDIV effect was sometimes more difficult to highlight than a COUNT effect in patients' noisy recordings, we considered that a patient with a positive COUNT effect in the condition of oriented attention responded positively to the active paradigm, even if no FOCvsDIV effect could be detected.

2.5 Statistical analysis

We computed sensitivity, specificity, positive and negative predictive values of the active paradigm, on the one hand, to dissociate MCS from VS patients as well as to distinguish MCS+ from other MCS- and VS (i.e. no-MCS+) patients and, on the other hand, to predict awakening (e-MCS) *vs* no awakening (persistent VS or MCS).

Classic Chi-square or Fisher's exact tests (for small samples), as well as odds ratios were used to assess independence between the ability of the patients to perform the active task (positive effects in ERP results) and other parameters like age, gender, the etiology of coma, the behavioral categorization at the time of recording and the outcome at six months.

3. Results

An effect of attention manipulation (FOCvsDIV) was observed in 9 patients. A significant difference between focused and diverted deviants was observed in 7 patients at the latency of the P3 response (FOCvsDIV P3) and in 2 other patients at the N2 latency (FOCvsDIV N2). For these 9 patients, a COUNT effect could also be detected at similar latencies. Besides, 5 patients with no effect of attention manipulation (no FOCvsDIV effect) showed however a significant P3 (n=4) or N2 (n=1) in the condition of focused attention (COUNT effect). The ERPs of these 14 (21%) responding patients (i.e. showing at least a COUNT effect) are shown in Figure 2. The full individual characteristics of these 14 responders are provided in Table 2.

In flowchart form, for the 68 patients tested, Figure 3 represents the results of the active test as well as the clinical observations at 6 months as a function of the initial clinical categories.

3.1 Consistency of the active test with clinical assessment at the time of recording

Positive responses to the active paradigm were not related to the age or gender of the patient, nor to the cause of coma (Table 3). Regarding the later, there was no significant relationship between the three main etiologies of coma (brain trauma, stroke and anoxia) and the outcome of the active test ($\chi^2 = 1.51$, $p = 0.47$).

Interestingly, we found no significant difference in test responses between coma and post-coma patients (Fisher's Exact Test $p = 0.55$; Odds-ratio = 1.67 (95% confidence interval: 0.49 – 5.64)). Contrary to what would be expected based on clinical assessment alone, 9 coma patients proved responding. The 5 other responders were post-coma patients (2 MCS+ and 3 MCS- patients).

In post-coma patients (N = 31), we found a significant relationship between the clinical category (VS, MCS- and MCS+) and the response to the active test (χ^2 = 9.80, p=0.002). Precisely, the distinction between VS and MCS (i.e. MCS+ or MCS-) patients was significantly correlated with test outcome (Fisher's exact test p = 0.011; Odds ratio = 0.05 (95% confidence interval: 0.002 – 0.99)). This reveals a significant link between the VS/MCS dichotomy and the outcome of the active test. Indeed, no positive response could be established among VS patients, while some MCS patients did respond positively. The correlation between the no-MCS+ (i.e. VS or MCS-) / MCS+ dichotomy and the result of the active test was not significant (Fisher's exact test p = 0.06; Odds ratio = 16.67 (95% confidence interval: 1.14 – 243.9)) but showed a tendency which goes the other way in the sense that being in a MCS+ is fairly predictive of a positive response.

3.2 Prognostic value of the active test

The outcome at six months after the active test was assessed in each patient both in terms of awakening (being in an e-MCS state or not) and functional dependencies using the GOS-E (a positive evolution corresponding to GOS-E > 2). Table 4 and Table 5 display the prognostic value of the active test for these two measures of clinical outcome in the different sub-populations.

Over the whole population, we found a strong correlation between the outcome of the active test and both awakening and functional dependency. For these two measures of functional outcome, the active test shows a high specificity and a high positive predictive value. This illustrates the fact that nearly all patients who responded positively to the active test did awake within the 6 months after the time of recording and showed a GOS-E > 2. Conversely, several patients who responded negatively to the tests did awake and showed a GOS-E > 2, hence the poor sensitivity and negative predictive values.

Similar results are obtained when restricting this assessment to post-coma patients. In these patients, responding positively to the active test is highly predictive of both awakening and good functional outcome. For both measures, the test shows a specificity and a positive predictive value of 1. No VS patients responded positively to the active test and only 4 among 17 obtained a GOS-E score greater than 2 after 6 months (3 were e-MCS). Conversely, 2 out of 3 MCS+ patients did respond positively to the test and all three were in an e-MCS after 6 months with a GOS-E score greater than 2. For the whole group of MCS patients as well as for MCS- patients only, the active test shows a specificity and a positive predictive value of 1, for both outcome measures. On the one hand, among the MCS patients who did not progress to e-MCS and a GOS-E score greater than 2, none had shown a positive active test. On the other hand, all MCS patients who succeeded in the active test, awoke and presented a GOS-E score greater than 2 after 6 months. In the MCS and MCS- populations, the active test also shows a significant correlation with the outcome in terms of awakening. This further reflects the fact that most MCS- patients who did not respond positively to the active test (7 out of 8) did not awake after 6 months.

Finally, in the coma population, all patients who succeeded in the active test (N = 9) were e-MCS and presented a GOS-E greater than 2 at 6 months, except for one patient who died early as a consequence of withdrawal of life sustaining treatment initiated independently of this study. This yields a high specificity and a high positive predictive value. However, the correlation between the outcome of the active test and the clinical outcome at 6 months is not significant.

4. Discussion

4.1 Main findings and conclusions

We used a new, recently validated task-based EEG test at bedside. This test rests on voluntary sustained attention and as such, it is cognitively demanding. In healthy subjects, it has been shown to be sensitive at the individual level (Morlet et al., 2017). In this study, we tested patients with disorders of consciousness for less than a year.

Most previous active paradigms investigated a possible discrimination between MCS and VS patients (Kondziella et al., 2016), considering that the former are more likely to follow commands. Accordingly, we found no responders among VS patients. A positive response to the test predicted to be MCS rather than VS and a negative response to the test was in favor of MCS- or VS rather than MCS+.

Beyond the population of chronic patients, it is essential to fully evaluate the relevance of such an active EEG test. In the whole population tested here, 14 patients (21%) showed a positive response with a positive predictive value of awakening (e-MCS) at 6 months of 93%. Strikingly, among responders, 10 patients were tested at the ICU within 1 month after coma onset and 9 of them were still in coma. This is of outmost importance as these results do not only fit with previous findings in chronic disorders of consciousness (Kondziella et al., 2016). They further demonstrate that preserved cognitive functions can be found also in coma patients. Our observations are in agreement with those of Claassen and collaborators (Claassen et al., 2019) although it is interesting to note that their test was based on the EEG response to a simple order. Based on fairly complex instructions, our test provides argument for the preservation of higher levels of cognition in these early-recorded patients. These findings suggest that cognition is not only dissociated from overt expression of awareness but also from overt arousal, thus highlighting the limits of behavioral assessments across the whole spectrum of DoC (Giacino and Edlow, 2019).

Importantly, when considering both coma and chronic patients, we found high positive predictive value (0.93) of the active test for awakening (e-MCS). However, the negative predictive value for awakening over the whole patient population was only 0.44. Among reasons for false negative results, a possible aphasia could have prevented the understanding of instructions. A focal lesion of the dominant hemisphere was an exclusion criterion but understanding or attention disorders independent from vigilance disorders cannot be excluded. Some patients could also have been so tired that they could not perform this demanding tasks over time. Finally, one cannot exclude that consciousness, and ability to respond to the task fluctuate within a day or a week in these patients.

This is an important reminder that a negative response to such an active test cannot be considered a marker of poor prognosis (Kondziella et al., 2016). Further studies should ideally repeat the test over several days.

Task-based EEG methods that can easily be applied at patient's bedside and improve prognostication of patients with acute brain injuries have great potential. It also raises questions about the differences and complementarities between alternative active EEG paradigms, and about the nature of the cognitive processes they probe (Bayne et al., 2020; Cecconi et al., 2020; Sergent et al., 2017).

There is no doubt that such paradigms will develop and expand, which already raises the critical question of how they should be incorporated into clinical practice (Giacino et al., 2018; Peterson et al., 2020).

Interestingly, the lack of responsiveness of the EEG to auditory and / or nociceptive stimuli does not appear to be a sufficient criterion for not performing an active test, as three responders had an areactive EEG. This could be explained by the fact that visual analysis of EEG reactivity is subject to great inter-rater variability (Duez et al., 2018) and cannot be considered as an isolated prognosis criterion. Besides, two responders also showed abnormal early evoked

potentials (patients 3 and 8). This suggests that these markers, when altered, should not prevent us from performing an active test. One could even extend this conservative reasoning to any (temporary) failure to detect a cortical response with EEG or any other means. Along this line, it has been argued that cortically mediated states, which are probably necessary but not sufficient phenomena for the emergence of consciousness, will more likely be detected as one diversifies the functional explorations (Naccache, 2018). The proposed test is original, promising and complementary of existing ones, as it is active and cognitively demanding. It can be operated at bedside and proved able to detect covert cognition in patients with disorders of consciousness of various etiologies and at various times after the onset of coma, including short-lived ones.

Cognitively as demanding as the EEG tasks typically used in brain-computer interfaces (BCI), a positive response to this test also inclines to attempt to communicate with these patients using a BCI (Luauté et al., 2015).

4.2 Limitations of the study

The main limitation of this study comes from its retrospective nature. In particular, we had to rely on the independent clinical evaluations made by medical experts, which it would have been useful to complement with complementary assessments (e.g. a CRS-R in coma patients). Future, prospective, studies could focus on either the diagnostic or prognostic value, or both, of the proposed active test, but importantly, they would enable a design where homogeneous subpopulations of patients could be thoroughly assessed and compared, possibly in a longitudinal fashion. Ideally, this would be part of a multicentric study so as to enable larger sample sizes. Note that the latter would likely require to develop a fully-automated data analysis, which is challenging but would definitely make a major step towards disseminating this kind of tests.

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Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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Figure legends

Figure 1: Experimental paradigm and expected responses.

A classic two-tone auditory oddball paradigm with frequency deviants was used. Standard and deviant stimuli were tone-bursts lasting 200 ms, including 20 ms rise-time and 20 ms fall-time. Pitch was 500 Hz for the standards, 1000 Hz for the deviants. The stimuli were regularly presented every 1010 ms. The deviants appeared randomly with a probability of 0.15. They were preceded by at least 2 standards.

The auditory oddball paradigm is presented in three attention conditions. 1) Mind wandering: a passive situation, without any instruction, 2) Diverted attention: instruction is given to perform a mental imagery task in order to keep attention away from the stimuli, 3) Focused attention: instruction is given to count deviant stimuli (33 deviants in the first block, 30 in the second block and 31 in the third one).

The 3 conditions were always presented in this particular order to the patients in order to limit the risk of inopportune deviant counting during passive listening and mental imagery. The whole recording session lasted about 30 min.

In each condition, expected responses are depicted by the grand average responses of twenty healthy subjects (from Morlet et al. Psychophysiology 2017). Responses to standards (thin lines) and deviants (thick lines) at the three midline electrodes are displayed in each attention condition: in blue for Mind wandering, in green for Diverted attention and in red for Focused attention. In the Focused attention condition, the COUNT effect (large P300 response resulting from voluntary implication in the counting task) is highlighted by significant differences observed at the group level between responses to standards and deviants at each electrode (horizontal grey bars). The rightmost box displays the FOC*vs*DIV effect: the difference

observed between responses to deviants in the FOCused condition (enhanced P300 response) and deviants in the DIVerted condition (reduced P300 response). This effect is highlighted by thick horizontal black bars displaying significant differences at the group level for each electrode (randomization test point by point with correction for multiple temporal tests).

Figure 2: Individual tracings of the 14 patients responding positively to the test

A positive test was defined by either a positive effect of counting deviants (COUNT effect) in the focused attention condition or a positive effect of attention manipulation (FOCvsDIV effect) between the condition of focused attention (counting deviants) and the condition of diverted attention (performing mental imagery task).

For each patient (numbered from 1 to 14 as in Table 2), the responses of interest at electrode Cz are shown:

- above the COUNT effect observed in the comparison between responses to standards (red thin line) and deviants (red thick line) in the condition of focused attention
- below the FOCvsDIV effect observed in the comparison between responses to deviants in the condition of focused attention (red thick line) and in the condition of diverted attention (green thick line).

As in the healthy population, we observed two distinct patterns: a classic P300 effect in centro-parietal regions (over Cz and Pz) and/or a less expected N2 effect in centro-frontal regions (over Fz and Cz) (see Morlet et al. Psychophysiology 2017). A two-step detection process was used at the individual level. First, an objective detection was performed using point-by-point permutation tests on the individual trials. In the second step, when the effect of attention was statistically significant, a trained neurologist validated the wave using visual waveform analysis.

Figure 3: Distribution of patients responding positively to the active paradigm as a function of their behavioral assessment at the moment of recording and their outcome at six months.

- In the second column: Clinical assessment at the moment of recording: coma, VS (vegetative state), MCS- (minimally conscious state minus), MCS+ (minimally conscious state plus)
- In the third column: Result of the active test: "TEST-" denotes patients showing no effect. "TEST+" denotes patients showing either positive COUNT effect alone or positive COUNT effect and positive FOCvsDIV effect. COUNT is the effect of counting the deviants in the condition of focused attention. FOCvsDIV is the differential effect between the deviants in the condition of focused attention and the condition of diverted attention. All patients with positive FOCvsDIV effect showed also positive COUNT effect.
- In the forth and fifth columns: Outcome at six months in terms of Glasgow Outcome scale (GOS-E in the forth column) and clinical assessment (in the fifth column). Patients with GOS-E = 1 died before arising from coma or vegetative state (VS). Some patients awoke and then died from independent reason within 6 months. For these patients, the score obtained at awakening was retained. They are counted with the symbol † in the fifth column. Patients assessed as e-MCS (exit minimally conscious state) were considered as awoke.

Figure 2

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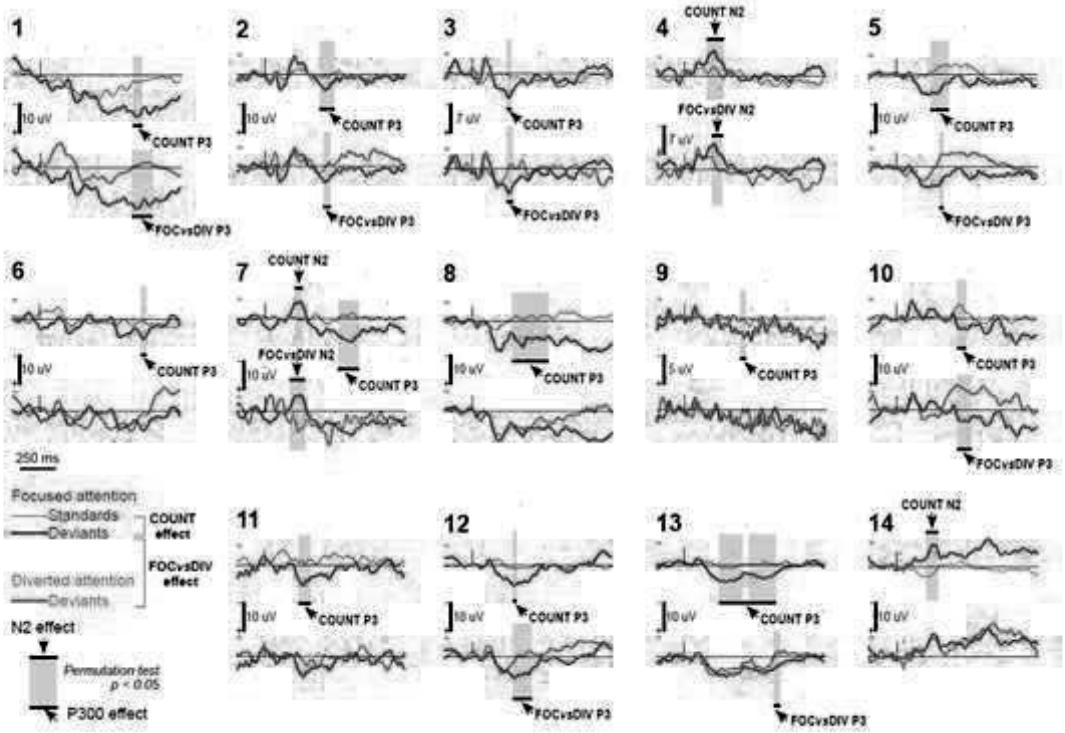

Figure 3

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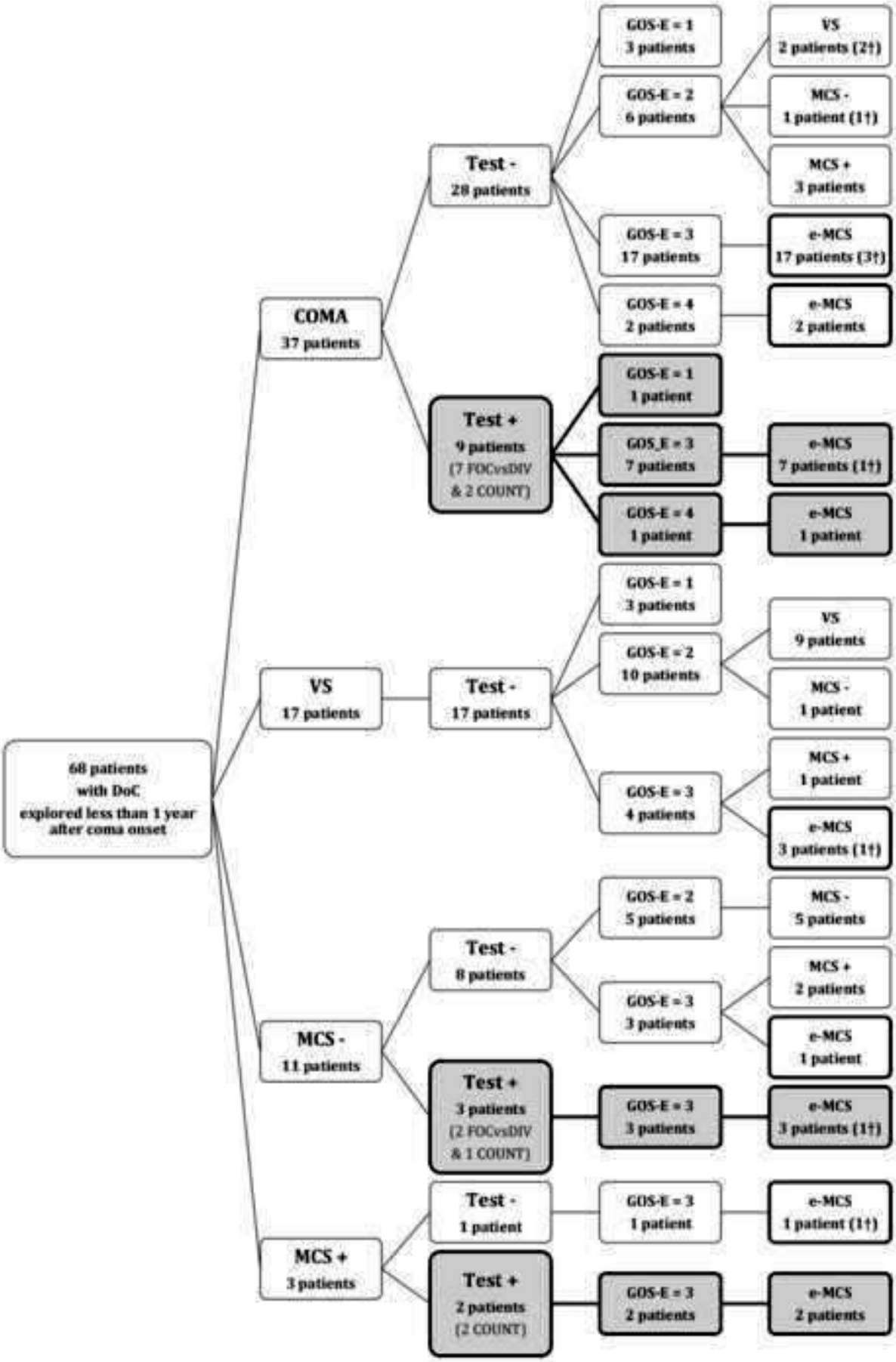

Figure 1

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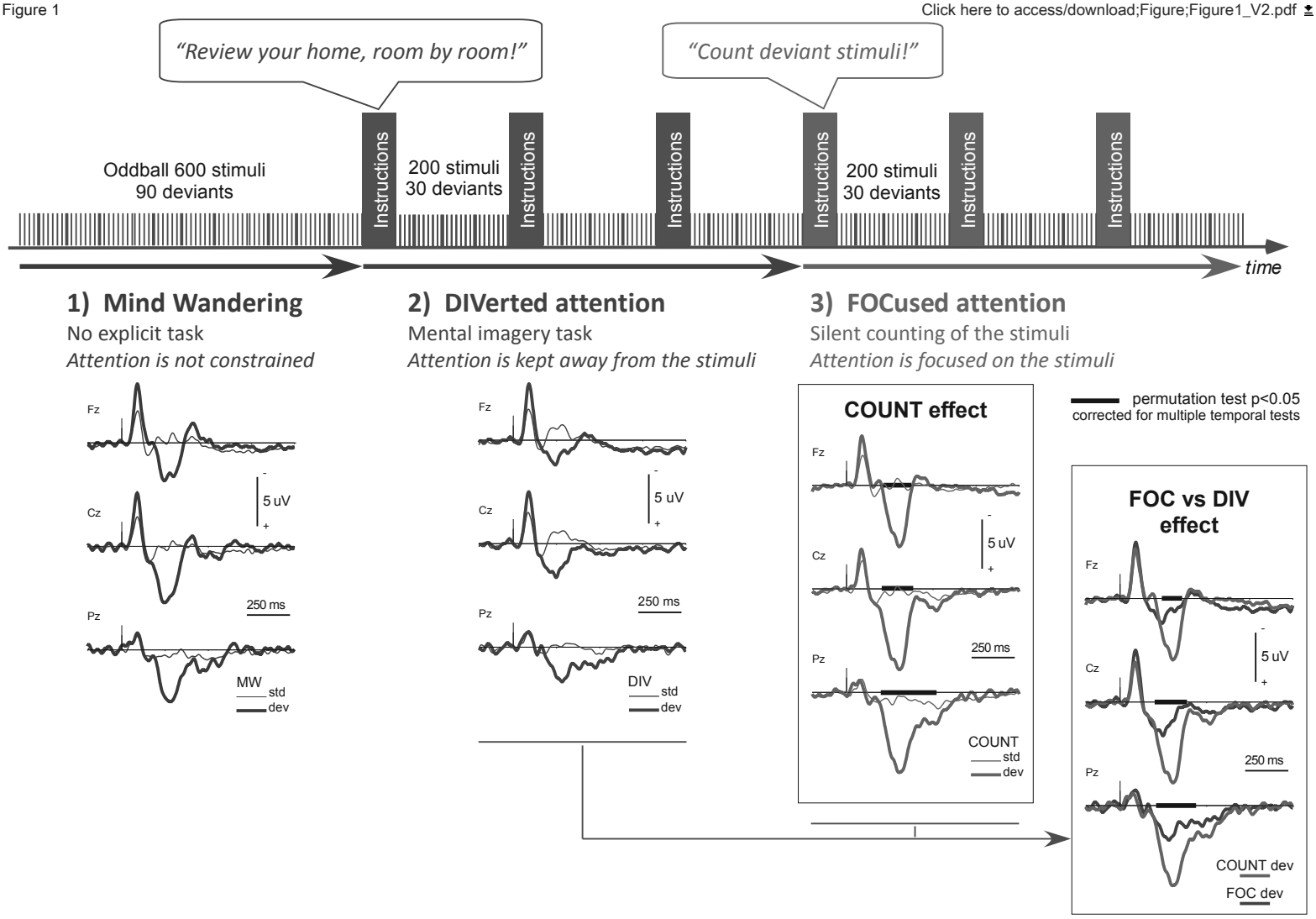


Table 1: Full description of the set of 68 patients.

			sub-acute or chronicDoC		
		Coma (n = 37)	**VS** (n = 17)	**MCS-** (n = 11)	**MCS+** (n=3)
Age mean ± sd (years)		53 ± 4	45 ± 21	41 ± 27	40 ± 6
Gender Female sex number (%)		17 (46%)	6 (35%)	3 (27%)	1 (33%)
Etiology nb of patients	Anoxia	9	8	2	0
	Brain traumatism	8	8	4	2
	Stroke	19	1	1	1
	Consequence of neurosurgery	1 [1]	0	2 [2]	0
	Other medical diagnosis	0	0	2 [3]	0
Delay from coma onset at the time of ERP recording					
mean ± sd		12 days ± 8	4.5 months ± 3.3	4.8 months ± 3.0	4 months ±5.6
range		2 - 33 days	1 – 10 months	23 days – 10 months	21 days – 10 months
Clinical score at the time of ERP recording		GCS	CRS-R	CRS-R	CRS-R
Median		6	4	8	8
range		2 - 9	3 - 8	4 - 11	6 – 10

For each sub-population: age, gender, distribution of the different etiologies, delay from coma onset and clinical evaluation at the time of EEG recording (assessed using the Glasgow Coma Scale for comatose patients, and the Coma Recovery Scale Revisited for patients with post-coma disorders of consciousness).

[1] subdural hematoma surgery

[2] frontal meningioma and craniopharyngioma surgery

[3] suicide attempted using insulin and tubercular meningitis

Table 2 Click here to access/download;Table;ClinNeurophy_Table 2.docx

Table 2: Individual characteristics of patients responding positively to the active paradigm

Patient # [1]	Age (years)	Gender	Coma etiology	Delay from coma onset at the time of ERP recording (d = days, m = months)	Behavioral state	GCS score	CRS-R score	EEG [2]	SSEP [3]	ML-AEP [3]	Anatomical lesions	Passive Novelty Oddball [4]	Active paradigm	GOS-E at six month [5]	Clinical status at 6 months
1	64	m	anoxia	2 d	coma	6		R	N	aN	Basal ganglia and bilateral insular cortex	N1	COUNT P3 FOCvsDIV P3	3*	Conscious, able to eat alone but confused before a secondary worsening with severe heart failure and death 2 weeks later
2	26	f	Stroke: left middle cerebral artery aneurysm	3 m	MCS-		8	R	N	N	Bilateral prefrontal and left frontal	MMN nP3	COUNT P3 FOCvsDIV P3	3	conscious with right hemiparesis and aphasia
3	69	m	Stroke: hypertensive Intracerebral hemorrhage	26 d	coma	7		R	aN	aN	Left parietal	N1	COUNT P3 FOCvsDIV P3	3	conscious with right hemiparesis, aphasia and secondary depressive syndrome
4	29	f	Stroke: pericallosal aneurysm	2 d	coma	9	3	R	N	N	Bilateral frontal	N1 nP3	COUNT N2 FOCvsDIV N2	3	Conscious with left spasticity
5	29	f	Stroke: spontaneous intracerebral hemorrhage	15 d	coma	9		R	NA	N	Right parietal	negative	COUNT P3 FOCvsDIV P3	3	conscious with left hemiparesis
6	62	m	Stroke: endovascular treatment of basilar artery aneurysm	5 d	coma	4		aR	N	aN	Intra-ventricular hemorrhage	N1 nP3	COUNT P3	3	Conscious with spatio-temporal disorientation
7	56	f	anoxia	14 d	coma	6		aR	N	N	NA	negative	COUNT N2 and P3 FOCvsDIV N2	1	No clinical sign of consciousness and limitation of life-sustaining treatment and death at day 22

8	21	f	brain trauma	25 d	MCS-	6	R	Abs	aN	Hemispheric and brainstem diffuse axonal injury	N1	COUNT P3	3	Conscious with left spastic hemiparesis and cognitive impairment (predominantly on verbal memory)
9	26	m	brain trauma	8 m	MCS-	8	R	Abs	N	Anterior callosal contusion Intraventricular hemorrhage	N1	COUNT P3	3	Conscious with cognitive and motor impairment
10	61	f	anoxia	17 d	coma	8	R	N	aN	NA	N1	COUNT P3 FOCvsDIV P3	3	Conscious without cognitive impairment but with severe motor disability
11	58	m	surgical treatment of subdural hematoma	12 d	coma	4	aR	NA	N	Left sub-dural	N1 nP3	COUNT P3	4	Conscious, with the same level of disability as before coma, related to Parkinson's disease
12	65	f	Stroke: anterior cerebral artery aneurysm	1 m	coma	7	R	N	N	Right frontal	N1	COUNT P3 FOCvsDIV P3	3	Conscious with akinetic mutism
13	69	m	craniopharyngioma surgery	3 m	MCS-	9	R	N	N	Corpus callosum and hydrocephalus	N1 nP3	COUNT P3 FOCvsDIV P3	3*	Conscious with severe cognitive impairment. Death at 5 months from septic shock (digestive door entrance)
14	28	m	brain trauma	10 m	MCS+	10	R	aN	NA	Right frontal contusion and hemispheric diffuse axonal injury	not available	COUNT N2	3	Conscious with cognitive impairment, left hemiplegia and right upper limb cerebellar tremor

GCS: Glasgow Coma Scale; CRS-R: Coma Recovery Scale Revisited; EEG: electroencephalogram; SSEP: somatosensory evoked potentials; ML-AEP: middle latency auditory evoked potentials.

[1] Same patient's numbering as in Figure 2

[2] R = reactive EEG, aR = areactive EEG (visual analysis by the neurophysiologist, in response to auditory and nociceptive stimuli)

[3] N = normal evoked responses, aN = abnormal evoked responses, Abs = absent responses, NA = result not available

[4] For details concerning the passive oddball paradigm, see Fischer et al (2008)[10]

[5] The asterisk for patients 1 and 13 means that the patient awoke (GOS-E = 3) and then died from independent reason less than six months after the onset of coma.

Table 3 : Comparison of patients' characteristics and their ability to perform the active test.

Characteristics of the patients	**Patients with positive test [1] n = 14**	**Patients with negative test [2] n = 54**	**Fisher's exact test**	**Odds ratio (95% CI)**
Age > 51 years [3]	8 (57%)	26 (48%)	p = 0.77 (NS)	1.44 (0.48 – 5.1)
Female sex	7 (50%)	20 (37%)	p = 0.54 (NS)	1.7 (0.54 – 5.38)
Cause of acute brain injury: brain traumatism	3 (21%)	19 (35%)	p = 0.52 (NS)	0.5 (0.14 – 1.82)
stroke	6 (43%)	16 (30%)	p = 0.36 (NS)	1.78 (0.48 – 5.55)
anoxia	3 (21%)	16 (30%)	p = 0.74 (NS)	0.65 (0.18 – 2.33)
Others	2* (14%)	3** (6%)	p < 0.001	102.0 (13.86 – 516.8)

* consequence of surgery (subdural hematoma and craniopharyngioma surgery)

** 1 frontal meningioma surgery and 2 other medical diagnosis

[1] A total of 14 patients were able to perform the active test, with at least positive COUNT effect, including 9 coma patients and 5 MCS patients.

[2] A total of 54 patients showed neither FOCvsDIV nor COUNT effect, including 28 coma patients, 9 MCS and 17 VS patients.

[3] 51 years was the median age in population.

Table 4: Prognosis value of the active test in terms of awakening in the different sub-populations.

A positive evolution corresponded to the e-MCS category at 6 months.

Active test	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**	**Accuracy**	**Fisher's exact test**	**Odds-ratio**
All (n = 68)	*0.30*	*0.96*	*0.93*	*0,44*	*0,63*	*F (p=0.005)*	*12.07 (1.473 – 98.91)*
Coma (n = 37)	0.30	0.90	0.89	0.32	0,38	F (p=0.39; NS)	3.789 (0.409 – 35.09)
Post Coma (n=31)	*0.50*	*1*	*1*	*0.81*	*0,84*	*F (p=0.001)*	*43.00 (2.050 – 902.1)*
VS (n = 17)	0	1	NA	0.82	0,82	NA	NA
MCS (n=14)	0.71	1	1	0.78	0,86	F (p=0.02)	33.00 (1.305 - 834.5)
MCS- (n = 11)	0.75	1	1	0,88	0,91	F (p=0.02)	35.00 (1.118 – 1096)
MCS+ (n=3)	0,67	NA	1	0	0,67	NA	NA

Table 5: Prognosis value of the active test in terms of dependence in the different sub-populations.

A positive evolution corresponded to a GOS-E>2 at 6 months.

Active test	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**	**Accuracy**	**Fisher's Exact test**	**Odds-ratio**
All (n = 68)	*0.33*	*0.96*	*0.93*	*0,50*	*0,59*	*F (p=0.005)*	*13.00 (1.587 – 106.5)*
Coma (n = 37)	0.30	0.90	0.89	0.32	0,46	F (p=0.39; NS)	3.789 (0.409 – 35.09)
Post Coma (n=31)	*0.38*	*1*	*1*	*0.69*	*0,74*	*F (p=0.008)*	*23.94 (1.183 – 484.5)*
VS (n = 17)	0	1	NA	0.76	0,76	NA	NA
MCS (n=14)	0.56	1	1	0.56	0,71	F (p=0.09; NS)	13.44 (0.575 – 314.5)
MCS- (n = 11)	0.50	1	1	0,63	0,73	F (p=0.18; NS)	11.00 (0.425 – 284.5)
MCS+ (n=3)	0,67	NA	1	0	0,67	NA	NA

SUPPLEMENTARY MATERIAL

I – Population

The active auditory ERP paradigm was used as part of the global neurophysiological evaluation in patients admitted in our hospital at the acute phase of coma in the absence of clinical sign of awareness 48h after sedative treatment suppression or for ad-hoc evaluation during a chronic disorder of consciousness. Every patient benefited from a first neurophysiological evaluation with EEG, somatosensory evoked potentials (SEPs) and brainstem and middle latency auditory evoked potentials (AEPs). EEG helps assess cortical responsiveness but also enables to treat possible epileptic seizures in coma patients before pursuing with further assessments. AEPs also permit to discard the presence of a major hearing impairment that could jeopardize the measure of auditory ERPs. Metabolic confounders were also treated before recording. In case of preserved somatosensory and auditory cortical responses, this basic evaluation was completed by passive (MMN and novelty P3) and active tests.

Major lesions of the dominant hemisphere, hearing loss or unfamiliarity with french language were exclusion criteria for the active test.

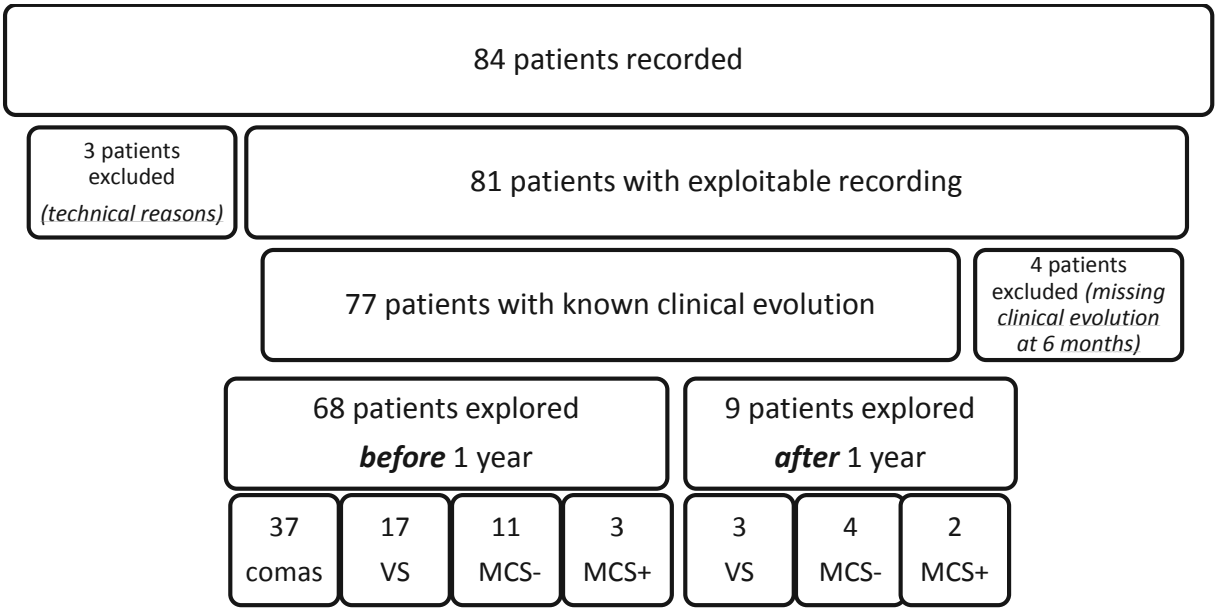
ERPs using the active paradigm were recorded with a large range of delays from coma onset in 84 unresponsive adults (see Figure S1). Three patients were excluded since ERP recordings were not exploitable for technical reasons. Four recorded patients were excluded since they were addressed to our hospital for a short period of 24 to 48h, specifically to perform a clinical and neurophysiological evaluation and we lost sight of them after the recording. Note that none of these lost patients showed a positive result to the active paradigm.

Nine patients were explored after 1 year. None of them had a positive response to the test.

The study focused on the 68 patients recorded before 1 year post-coma and considered a clinical outcome at 6 months of follow-up determined with the Glasgow Outcome Scale Extended (GOS-E) and in terms of awareness level.

Thirty-seven of the 68 patients included in the study were recorded at the acute phase of coma, at least 48 h after a sedative treatment break and at the latest 33 days after coma onset (mean delay from coma onset: 12 +- 8 days). The other 31 patients showed post-coma disorders of consciousness: 17 were in a vegetative state, 3 were characterized as MCS+ and 11 as MCS-.

Figure S1: Patients' enrolment



In the total set of 77 patients, initial coma was post-anoxic in 20 cases, post-traumatic in 28 cases, and consecutive to stroke in 24 cases. It followed a neurosurgical brain intervention in 3 cases and another medical pathology in 2 cases.

II - Outcome assessment

Functional outcome at six months after recording was determined using the CRS-R and the Glasgow Outcome Sale Extended (GOS-E) (Fayol et al., 2004) whose categories are as follows:

1 – Death.

2 – Persistent vegetative State or lack of response to simple commands. This category includes MCS-.*

3 – Severe disability, lower. Requires frequent help of someone to be around at home most of the time every day. This category includes MCS+.

4 – Severe disability, upper. Can be left alone more than 8 hours during the day, but unable to travel and/or go shopping without assistance.

5 – Moderate disability, lower. Unable to work or only in sheltered workshop.

6 – Moderate disability, upper. Reduced work capacity; Resumes less than 50% of the pre-injury level of social and leisure activities.

7 – Good recovery, lower.

8 – Good recover, upper.

*As the GOS-E does not distinguish between VS, MCS- and MCS+, we classified these different states as follows: VS and MCS- were grouped and entered the GOS-E 2 category, whereas MCS+ was classified as GOS-E 3. Indeed, patients are considered in the GOS-E 2 category when they are unable to respond to simple orders, which also defines the distinction between MCS- and MCS+

Reference

Fayol, P., Carrière, H., Habonimana, D., Preux, P.-M., Dumond, J.-J., 2004. Version française de l'entretien structuré pour l'échelle de devenir de Glasgow (GOS) : recommandations et premières études de validation. Annales de Réadaptation et de Médecine Physique 47, 142–156. https://doi.org/10.1016/j.annrmp.2004.01.004