Neurophysiological assessment for evaluating residual cognition in vegetative and minimally conscious state patients: a pilot study

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Summary

The aim of this study was to assess residual cognitive function and perform outcome evaluation in vegetative state (VS) and minimally conscious state (MCS) patients, using Neurowave, a system able to monitor event-related potentials (ERPs) induced by neurosensory stimulation.
Eleven VS and five MCS patients underwent neurological examination and clinical evaluation performed using validated clinical and behavioral scales; they also underwent neurosensory stimulation, which consisted of administration of target images (rare stimuli), relevant to the patient's personal history and having emotional significance, alternated with non-target images ("standard" stimuli), which had no emotional significance. All simultaneous ERP responses at baseline (T0) and at three months from T0 (T1) were recorded.
At T0 we found significant differences between the VS and MCS patients for the N200 (p=0.02) and P300 (p=0.04) waves. The neurophysiological analysis at T1 showed a significant difference only for P300 (p=0.02), probably due to the improvements observed in the VS subjects for the N100 (p=0.009) and N200 (p=0.02) sensory components.
Our findings seem to show the value of ERP monitoring in VS and MCS patients as a means of investigating residual cognitive function. This approach could guide early therapeutic and rehabilitation interventions, and contribute to identifying better diagnostic and prognostic markers for use in unresponsive or low-responsive patients.

KEY WORDS: cognitive assessment, event-related potentials, minimally conscious state, outcome evaluation, vegetative state, visual stimuli.

Introduction

The Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) and the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) are conventional consciousness assessment scales according to which a patient with severe brain injury must display overt motor responses to command in order to be considered aware. Patients who appear to be awake but show no external evidence of awareness are instead considered to be in a vegetative state (VS) (The Multi-Society Task Force on PVS, 1994). Conversely, those showing limited but clear evidence of awareness of self or of environment, on a reproducible or sustained basis (Laureys et al., 2004), can be diagnosed as minimally conscious. However, given that responses to command may be only minimal or inconsistently present they can be very difficult to identify clinically; this difficulty may be a main factor contributing to the ~40% misdiagnosis rate for VS (Schnakers et al., 2009). In recent years, however, there has been a growing awareness that absence of behavioral evidence of command-following does not necessarily indicate that a patient is truly devoid of awareness or of the ability to follow commands under appropriate conditions (Cruse et al., 2011). The most promising neurophysiological method for evaluating the possible presence of general cognitive functioning in disorders of consciousness (DOC) patients is the measurement of event-related potentials (ERPs) (De Salvo et al., 2012; Steppacher et al., 2013). Even though ERPs provide an important quantitative non-invasive means of obtaining information about cortical signal processing (Gratton et al., 1990), they are used not just to probe consciousness but, in particular, to investigate the functional status of the brain. ERP studies focusing on behavioral aspects have frequent-

ly examined four specific components: N100, N200, P300 and N400. Most unconscious patients show the N100 and N200 components (Connolly et al., 2000; Duncan et al., 2009). The N100 is an index of sensory/perceptual functions during visual, auditory and somatosensory processing. The latency of the N100 component is a measure of the time required for sensory and cognitive processing of visual stimuli. The N200 has been linked to perceptual processing of deviant stimuli that occurs below the level of consciousness. Visual stimuli have been reported to elicit the highest N200 amplitudes over the preoccipital region (Simson et al., 1977). The N200 component has been shown to vary according to the type of task (semantic vs physical discrimination) (Ritter et al., 1983) and type of stimulus presented, such as written words, pictures of objects, or human faces. The P300, which also occurs in response to deviant or oddball stimuli, is thought to reflect higher-level processing, such as immediate memory. The most important of these components is the P300, which appears in many cases in response to target stimuli to which the subject is paying attention. However, it is known that the P300 also occurs, with smaller amplitudes, in passive paradigms, where the subject is not required to pay attention to specific stimuli, as well as in unconscious coma patients. With regard to memory, the P300 wave seems to be sensitive to several cognitive functions such as stimulus recognition and subjective significance and working memory updating (Polich 2007; Holeckova et al., 2006). Among the candidate indicators of higher cognitive functions, the P300 may probably be considered one of the most important (Kotchoubey, 2005; Faugeras et al., 2011).
Data from the literature show that patient-specific stimuli are able to activate specific cerebral cortical systems (the primary sensory circuits, the attention and motor imagination circuits) (De Salvo et al., 2012). Moreover, intensive programs of neurosensory stimulation can facilitate recovery of cognitive function.
In response to simple auditory stimulation, minimally conscious state (MCS) patients, compared with VS patients, have been found to show spatially larger activation areas, suggesting that they show more distributed higher cognitive processing and integration of auditory stimuli (Laureys et al., 2004).
Neurowave (Khymeia s.r.l., Padua) is an innovative and technologically advanced device that allows the programming and automated administration of sensory stimuli (such as images, movies and sounds, including patient-specific recordings) and the simultaneous monitoring of multiple biophysiological signals.
The aims of this study were to monitor visual ERP components detected in a group of DOC patients during neurosensory stimulation, and ultimately to correlate these components with the outcome of the clinical assessment performed using the gold-standard CRS-R. This longitudinal pilot study could potentially prove important, if it leads to the introduction of an objective measure for assessing responses to visual stimulation in patients undergoing neurosensory rehabilitation. We suggest that clarification of the extent of changes in the clinical indices assessed could help in the development of an integrated protocol for the assessment of patients with DOC.
In addition, to our knowledge, this is the first longitudinal study based on the use of visual neurosensory stimulation and simultaneous recording of ERPs performed using the Neurowave system.

Materials and methods

Study population

We enrolled sixteen subjects (10 males and 6 females) with a mean age of 53.81±12.83 years. The VS group consisted of 11 subjects (6 males and 5 females, mean age 58.10±11.38 years), whereas the MCS group consisted of five subjects (4 males and 1 female, mean age 44.4±11.50 years). The patients were studied at between five and 24 months after brain damage and met the internationally established criteria for a diagnosis of VS or MCS. Demographic, etiological and neurophysiological data are shown in table I.
Patients with unstable clinical conditions or a previous history of neurological, visual or psychiatric disorders were excluded. All patients underwent at least one brain computed tomography or magnetic resonance imaging scan (Fig. 1). No psychotropic drugs were being administered during the period of ERP recording. All the patients showed normal or slightly delayed visual evoked responses. All the eligible patients were assessed at two time points by careful neurological and neurophysiological evaluation: at baseline (T0) and three months after T0 (T1). At baseline, all the subjects underwent a neurological examination and clinical evaluation performed using validated clinical and behavioral scales, namely the GCS, the Glasgow Outcome Scale (GOS), the Disability Rating Scale (DRS), the Levels of Cognitive Functioning scale (LCF) and the CRS-R (Table II). The present study was approved by the Ethics Committee of IRCCS Centro Neurolesi "Bonino-Pulejo" and written informed consent was obtained from the legal guardians of all the patients.

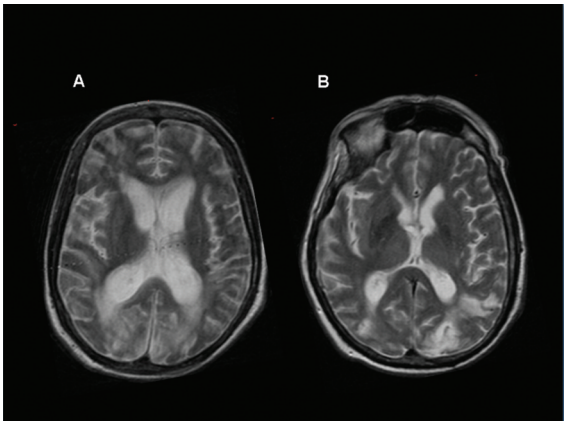

Figure 1 - MRI findings: illustrative example of T2-weighted MRI in an MCS (A) and VS (B) patient.

Neurophysiological examinations

The patients included were stimulated using the Neurowave system, which provides for simultaneous acquisition of ERPs. It allows a quantitative investigation of ERPs/electroencephalogram reactivity in DOC patients and the creation of experimental protocols aimed at identifying residual cortical function by electrophysiological assessment.

ERPs were recorded from six Ag/AgCl electrodes, four placed above the midline of the scalp (Fz, Cz, Pz, Oz) plus T3 and T4, in accordance with the international 10/20 system, and referred to linked earlobes with a forehead ground. Electro-oculograms were recorded

Table I - Demographic, neurophysiological characteristics of patients with disorders of consciousness at T0 and T1.

Patients	Age (y)	Gender	Etiology	Months from injury	N100 (T0)			P300 (T0)			N100 (T1)			P300 (T1)		
					Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
VS 1	70	F	Subarachnoid hemorrhage	9	180	180	153	/	/	/	141	138	138	/	/	/
VS 2	48	M	TBI	10	126	126	126	326	353	348	99	103	106	336	333	341
VS 3	43	F	Anoxia	12	133	126	130	/	/	/	123	118	123	/	/	/
VS 4	44	M	TBI	12	140	145	145	/	/	/	140	142	145	/	/	/
VS 5	50	M	Subarachnoid hemorrhage	24	158	158	160	/	/	/	160	160	162	/	/	/
VS 6	71	M	Anoxia	10	174	174	173	/	/	/	168	170	172	/	/	/
VS 7	63	M	Subarachnoid hemorrhage	8	/	/	/	/	/	/	/	/	/	/	/	/
VS 8	64	F	Anoxia	6	150	152	150	360	357	360	147	148	147	350	352	350
VS 9	50	M	Subarachnoid hemorrhage	6	152	154	154	/	/	/	150	152	152	/	/	/
VS 10	62	F	Subarachnoid hemorrhage	5	144	145	145	340	344	344	140	142	142	340	342	342
VS 11	74	F	Subarachnoid hemorrhage	6	/	/	/	/	/	/	160	162	162	/	/	/
MCS 1	30	M	Subarachnoid hemorrhage	24	145	145	145	368	372	376	138	130	133	341	336	341
MCS 2	52	F	Subarachnoid hemorrhage	10	153	145	141	388	388	388	123	141	145	365	372	372
MCS 3	34	M	Subarachnoid hemorrhage	24	130	135	137	340	340	340	125	127	130	325	325	327
MCS 4	51	M	Subarachnoid hemorrhage	8	147	147	150	360	363	365	140	142	143	342	343	345
MCS 5	55	M	Anoxia	10	155	157	158	345	347	347	155	157	158	347	347	347

Abbreviations: N100, P300=ERP components; VS=vegetative state; MCS=minimally conscious state; TBI=traumatic brain injury.

Table II - Clinical scores of patients with disorders of consciousness at T0 and T1.

Patients	T0					T1				
	GCS	GOS	LCF	DRS	CRS-R	GCS	GOS	LCF	DRS	CRS-R
VS 1	8	2	3	19	5	9	2	3	20	7
VS 2	8	2	3	25	11	9	2	3	25	11
VS 3	9	2	2	25	6	10	2	3	25	9
VS 4	8	2	3	19	5	9	2	3	19	8
VS 5	9	3	3	24	11	10	3	3	23	12
VS 6	8	2	2	24	5	9	2	3	24	6
VS 7	9	2	3	23	9	9	2	3	23	9
VS 8	8	2	3	24	16	8	2	3	24	16
VS 9	9	2	2	24	7	9	2	2	24	12
VS 10	9	2	2	24	12	10	3	3	23	14
VS 11	9	2	3	26	6	9	2	2	26	6
MCS 1	11	3	3	19	16	11	3	3	19	16
MCS 2	10	2	3	24	14	11	3	3	23	16
MCS 3	9	2	3	25	11	11	3	3	24	14
MCS 4	11	2	2	27	10	11	3	3	23	14
MCS 5	11	2	3	20	10	11	3	3	19	12

Abbreviations: VS=vegetative state; MCS=minimally conscious state; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Scale; DRS=Disability Rating Scale; LCF=Levels of Cognitive Functioning scale; CRS-R=Coma Recovery Scale – revised; VS=vegetative state; MCS=minimally conscious state.

with four electrodes: the reference electrode plus one placed lateral to the outer canthus and one above and one below the left eye.
Patients (with eyes open) were positioned with their head turned toward the monitor displaying the visual stimuli. Throughout the stimulation time, the patients were carefully observed by the operator. In addition, their eye tracking was monitored by a camera (part of the Neurowave system) in order to better identify when they were fixating/not fixating the screen.
Data were digitized at a sampling rate of 256 Hz and filtered with a band-pass of 0.15-30 Hz. A notch filter was used.
The neurosensory stimulation consisted of the administration of target images (two rare stimuli), relevant to the patient's personal history and having emotional significance for him/her, alternated with non-target images (two "distractor" stimuli) which had no emotional significance. Both types of stimulus (standard and emotional image) were delivered for a duration of 500 ms. The inter-stimulus interval was set at 800 ms. The rare stimulus was programmed to occur in 20% of the trials and the images to appear in a random order. Patients underwent three stimulation sessions per week. Each session lasted 30 minutes. Subjects received a total of 500 stimulus presentations per session: each distractor image was presented 200 times and each rare image 50 times. Epochs with artifacts were identified, marked manually and excluded from ERP analysis. Indeed, we did not consider recordings where the patients did not fixate on the screen during the stimulation period (moments when patients were not fixating images on the screen were marked by the operator on the monitor) or where their movements resulted in multiple artifacts making the traces illegible. Recordings in which the patients closed their eyes were also excluded. The number of target trials remaining after rejection of those with artifacts, in particular those in which patients did not fixate on the screen, ranged from 34 to 38 images. We analyzed the ERPs in response to the rare stimuli. The Neurowave Reader software was used for ERP analysis. We used a semi-automatic method for rejection of trials with artifacts and trials with a voltage of ± 100 μV in any EEG channel.

Statistical analysis

We considered two different types of data: the clinical test scores (GCS, GOS, LCF, DRS, CRS-R) and the peak latencies from the times of the stimulus onset. Statistical analysis was performed on averaged traces from each participant using the R 3.0 software package. Where appropriate, the one- or two-tailed Wilcoxon signed-rank test was used for comparisons between T0 and T1 within the same group (VS and MCS) (intra-group analysis); instead the comparison between the two groups (inter-group analysis), at T0 and T1, was performed considering the mean of the Mann-Whitney U test. To avoid having to discard information due to the absence of waves, we decided to apply an adequately high threshold on the latencies when performing the statistical group comparisons. A latency threshold of 1000 ms (chosen after computing a sequence of tests) was taken to indicate absence of ERP components. The Fisher exact test was used to analyze dichotomous variables which indicated presence or absence of latencies. A p-value of <0.05 was taken as the level of significance.
The numerical data are presented as means and standard deviations when they show a Gaussian distribution, and as the median and first and third quartiles in the case of non-normal distribution.

Results

We compared the clinical test scores and peak latencies at baseline (T0) and after three months (T1) in each group (VS and MCS). As regards the clinical scores, the results of the intra-group analysis revealed a significant difference in GCS ($p=0.005$) and CRS-R ($p=0.01$) scores in the VS patients, and significant differences in GOS ($p=0.04$) and CRS-R ($p=0.04$) scores in the MCS group. The inter-group analysis results showed significant differences between VS and MCS patients only for GCS ($p=0.004$) at T0, and for GCS ($p=0.001$), GOS ($p=0.004$) and CRS-R ($p=0.02$) at T1, as shown in table III.
The intra-group analysis of ERP values revealed significant differences for N100 ($p=0.009$) and N200 ($p=0.02$) only in the VS group, and no significant differences in the MCS group.
From the inter-group analysis of ERP values, we observed significant differences for N200 ($p=0.02$) and P300 ($p=0.04$) at T0, and for P300 ($p=0.02$) at T1 (Fig. 2). These results were also confirmed by the Fisher exact test, which showed statistically significant differences for N200 ($p=0.013$) and P300 ($p=0.013$) at T0, and for P300 ($p=0.013$) at T1, as shown in table IV.

Discussion

The use of neurophysiological techniques to evaluate residual cognitive function in VS and MCS patients is a widely debated topic (Lehembre et al., 2012). The detection of cognitive waves (such as N100, N200, P300) in such patients should induce the neurophysiologist to persevere with this approach, using different modalities of stimulation.
In a recent work (Cavinato et al., 2009), a classical two-stimulus oddball task was used to elicit the P300; the patient's own name was used as the deviant and a pure tone as the standard stimulus. The authors found the P300 to be a potential predictor of recovery of consciousness in VS. This finding is in line with the results of several studies that have confirmed the utility of the P300 response evoked by deviant tones in

predicting awakening and favorable outcome from coma and VS (Cavinato et al., 2009). In another study, the same authors (Cavinato et al., 2011) continued to use the "subject's own name" paradigm, but added an "other first name" paradigm. It was found that in five out of 11 VS patients, a reliable P300 component could be observed in both conditions. These findings corroborate earlier reports showing that some patients in VS generate a P300 wave. The MCS patients, compared with those in the VS, exhibited

Table III - Intra- and inter-group differences in clinical scores at T0 and T1 in the vegetative state and minimally conscious state groups.

		VS Median (first-third quartile)	MCS Median (first-third quartile)	p-value (Mann-Whitney U)
GCS	T0	9.00 (8.00 – 9.00)	11.00 (10.00 – 11.00)	0.004**
	T1	9.00 (9.00 – 9.50)	11.00 (11.00 – 11.00)	0.001**
p-value (Wilcoxon)		0.005**	- 0.18	
GOS	T0	2.00 (2.00 – 2.00)	2.00 (2.00 – 2.00)	0.62
	T1	2.00 (2.00 – 2.00)	3.00 (3.00 – 3.00)	0.004**
p-value (Wilcoxon)		0.5	0.04*	
LCF	T0	3.00 (2.00 – 3.00)	3.00 (3.00 – 3.00)	0.57
	T1	3.00 (3.00 – 3.00)	3.00 (3.00 – 3.00)	0.37
p-value (Wilcoxon)		0.21	- 0.5	
DRS	T0	24.00 (23.5 – 24.5)	24.00 (20.00 – 25.00)	0.95
	T1	24.00 (23.00 – 24.5)	23.00 (19.00 – 23.00)	0.14
p-value (Wilcoxon)		0.39	0.05	
CRS-R	T0	7.00 (5.5 – 11.00)	11.00 (10.00 – 14.00)	0.1
	T1	9.00 (7.5 – 12.00)	14.00 (14.00 – 16.00)	0.02*
p-value (Wilcoxon)		0.01*	- 0.04*	

Abbreviations: VS=vegetative state; MCS=minimally conscious state; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Scale; DRS=Disability Rating Scale; LCF=Levels of Cognitive Functioning scale; CRS-R=Coma Recovery Scale-Revised; SD=standard deviation.
*p<0.05; **p<0.01.

Figure 2 - ERP findings: latencies of N100, N200 and P300 component of ERPs.
(a) MCS patient at T0, (b) VS patient at T0, (c) MCS patient at T1, (d) VS patient at T1. The relevant ERP is the black line, which is the difference wave between the green and purple lines. Legend: * = N100; + = N200; x = P300.

significantly longer P300 latencies for the "subject's own name" and the "other first name" paradigms. The authors argued that the finding of increased P300 latencies for more complex and salient paradigms in MCS but not in VS might help in the difficult differential diagnosis of MCS vs VS. Therefore, such results suggest that these types of stimulation should be integrated within clinical and research protocols, in order to increase their diagnostic and prognostic potential.

Our results also seem to support the value of this kind of approach, given that they seem to provide objective evidence of greater accuracy of ERPs versus clinical assessment. At baseline we found significant differences between VS and MCS groups both for the N200 (p=0.02) and P300 (p=0.04) waves; conversely, as regards the clinical scales, only the GCS scores (p=0.004) were able to distinguish between the two groups.

The analysis of the neurophysiological data, collected at the beginning of the study and three months after visual neurosensory stimulations with Neurowave, showed, at T1, no significant difference between the VS and MCS groups for any wave except for the P300 (p=0.02); no difference was recorded for N100 (p=0.009) and N200 (p=0.02) probably due to the improvements shown, in these waves, by the VS patients. In fact, between T0 and T1 there was a significant decrease in the number of N200 absent latencies (from 8/11 to 3/11), and a significant decrease in the N100 average value (from 151.11 ms to 143.50 ms). Moreover, the Fisher's exact test results confirmed that the absence of an ERP component could be a distinctive marker between a vegetative and a minimally conscious state. In particular, latency modulation of the P300 in MCS patients could indicate integrity of some higher cognitive processes and reflect relatively strong initial target stimulus processing associated with consciousness and self-cognition. Although the results of our study showed a statistically significant improvement of the clinical conditions of the patients in both in the VS and in the MCS group, some considerations need to be made given the emergence of differences between the two groups. First, the VS patients, compared with those affected by MCS, constituted a larger group with higher clinical variability. Second, our MCS sample did not present a traumatic etiology and showed a longer disease duration compared with the VS group.

Nevertheless, the improvement of the GCS scores in the VS patients (p=0.005) was not so great as to avoid the significant difference between the two groups at T1 (p=0.001). On the contrary, the significant improvement in the GOS scores (p=0.04) recorded by the MCS patients between T0 and T1 probably explains the significant difference between VS and MCS patients found at T1 (p=0.004), but not at T0 (p=0.62).The improvement in the GCS and GOS scores, probably related to the fact that these scales evaluate patients in a more global fashion, is an interesting result, but the improvement in the CRS-R scores is more interesting, given the purposes of our study. Indeed, the results recorded on that scale showed a statistically more significant improvement in the VS patients (p=0.01) than in the MCS patients (p=0.04), which led to a significant difference between the two groups at T1 (p=0.02). The CRS-R scale, in fact, has a more complex structure which was able to identify the slight improvements shown by the VS patients as a result of the treatment with Neurowave – improvements also highlighted by ERPs. However,

Table IV - Intra- and inter-group differences in ERP values at T0-T1 in the vegetative state and minimally conscious state groups.

ERP components	Times	Patients	Presence	Absence	Tot	p-value (Fisher's exact test)
	T0	MCS	5	0	5	0.46
		VS	9	2	11	
N100		Total	14	2	16	
	T1	MCS	5	0	5	0.69
		VS	10	1	11	
		Total	15	1	16	
	T0	MCS	5	0	5	0.013*
		VS	3	8	11	
N200		Total	8	8	16	
	T1	MCS	5	0	5	0.30
		VS	8	3	11	
		Total	13	3	16	
	T0	MCS	5	0	5	0.013*
		VS	3	8	11	
P300		Total	8	8	16	
	T1	MCS	5	0	5	0.013*
		VS	3	8	11	
		Total	8	8	16	

Abbreviations: MCS=minimally conscious state; VS=vegetative state. *p<0.05; **<0.01. The absent latencies were set at 1000 ms.

these clinical scales are qualitative measures subjectively interpreted by the physician. In fact, our study highlights the need to associate the clinical evaluation with neurophysiological methods in order to achieve a more objective diagnosis and accurate prognosis of DOC patients.

Even though the patients did not show a very strong clinical improvement during the rehabilitation treatment, some evidence could be can nevertheless be drawn from the neurosensory stimulations and simultaneous recordings of ERPs performed using Neurowave. Indeed, this system offers: i) biophysiological monitoring of the severely brain-injured patients with the possible identification of channels of communication and prognostic signals; ii) obvious advantages in terms of the quality and effectiveness of rehabilitation (in particular, early initiation of the rehabilitation program, made possible by Neurowave, promotes recovery probably related to the innovative method of multisensory stimulation, which is "tailored" to the single patient; iii) quantitative analysis of correlations between sensory stimulation and changes in the clinical status of patients. The main limitations of this pilot study, however, are probably related to the small sample size and to the clinical heterogeneity of the patients, and the fact that they were not stimulated for a long period of time. This may, indeed, explain why the level of clinical improvement recorded in the subjects was not particularly high; therefore, this treatment, which is highly innovative in the DOC field and needs to be encouraged, should be administered for longer periods of time. In addition, the lack of comparison with other similar works is due to the fact that the present study is among the first, in the field of DOC, to have tried using visual stimulation involving the use of targets that have emotional significance for the subject.

The main aim of the use of ERPs in this field is to seek to identify markers that could, potentially, have the capacity to discriminate between different impaired consciousness conditions. Our study showed that the ERP components examined herein occur more frequently in MCS than in VS patients. Our results also showed an improvement in some ERP components after Neurowave stimulation in VS patients, a finding reflected by CRS-R score improvements at follow-up.

On the basis of this study it might be argued that the P300 wave could be a potential positive predictor of the clinical outcome of DOC patients.

To our knowledge, this is the first study in this population involving visual neurosensory stimulation and simultaneous recording of ERPs performed using Neurowave, and the results highlight the role it could play in identifying better diagnostic and prognostic markers for use in unresponsive or low-responsive patients.

While we are aware of the limits deriving from the nature of this study (a pilot study), our findings seem to confirm the potential value of paraclinical testing based on ERPs.

Future investigations should perform longitudinal measurements in a more representative sample of patients in order to validate the predictive value of visual ERPs in the follow-up of DOC, and assess whether and in what way clinical factors (such as etiology and brain lesions) might affect the different characteristics of ERPs and the relevance of these factors in the management of these critical clinical conditions.

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