

Assessment of mismatch negativity and P300 response in patients with disorders of consciousness

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Abstract. – OBJECTIVE: To evaluate changes in mismatch negativity (MMN) and P300 response in vegetative state (VS) and minimally conscious state (MCS) patients before and after treatment, and their value for prediction of prognosis.

PATIENTS AND METHODS: Event-related potentials (ERPs), performed on 11 patients classified as VS (n = 6) or MCS (n = 5), and five healthy participants (i.e., control group). We performed a six months telephone follow-up to monitor changes in consciousness recovery.

RESULTS: Comparison of the three groups showed significantly higher MMN latency elicited by salient stimuli and P300 elicited by the subject's own name for the VS group, as well as significant difference in amplitudes of MMN elicited by frequent stimuli and P300 elicited by other first names for this group. The source of MMN and P300 responses was the frontal lobe for the control group, and temporal lobe for the VS and MCS groups.

CONCLUSIONS: The sudden increase in MMN amplitude and latency shortening may indicate an improvement in the state of consciousness. Neurophysiological evaluations suggest that patients with vegetative state (VS) and minimally conscious state (MCS) may preserve patterns of higher-order cerebral processing similar to those observed in conscious patients.

Key Words:

Consciousness disorder, Coma Recovery Scale Revised, Event-related potentials, Minimally conscious state, Vegetative state.

Abbreviations

VS: vegetative state; MCS: minimally conscious state; UWS: unresponsive wakefulness syndrome; ERPs: event-related potentials; DOC: disorder of consciousness;

MMN: Mismatch Negativity; CRS-R: Coma Recovery Scale-Revised; BAEP: Brainstem Auditory Evoked Potentials; N/A, not applied.

Introduction

Disorders of consciousness are common symptoms after brain injury and among them vegetative state (VS) and minimally conscious state (MCS) are frequently observed. Patients with MCS have severely impaired consciousness content and significantly decreased consciousness clarity, but still show minimal, yet specific, preservation of self or environmental awareness, as well as voluntary eye-opening and sleep-wake cycles. Although conscious behavioral activities are not continuous, these are reproducible or can be maintained long enough to be differentiated from primitive reflexive behaviors^{1,2}. MCS is significantly different from VS; although the patient's consciousness level is far from being stable or allow the capacity for mutual communication, there is robust evidence for behaviors showing self or environmental awareness. The next stage of recovery for MCS patients is to be awakened. However, VS or MCS can last a very long time, even until the patient's death³. Currently, evaluation of consciousness disorders mainly relies on clinical manifestations of patients, as well as in various assessment scales. The Coma Recovery Scale-Revised (CRS-R) is an internationally recognized VS assessment scale⁴, which can be used to evaluate multiple aspects of patients in a vegetative state, including auditory, visual, perception, movement, communication, as well as

to reflect symptom changes in patients in a more sensitive manner. Therefore, this is the main method used to diagnose, track, and evaluate MCS in clinical research. However, such clinical scales are highly subjective, and have difficulties in reflecting subtle changes in consciousness. On the other hand, nerve electrophysiology assessments possess certain advantages for the evaluation of patients with consciousness disorders because of their strong objectivity and high temporal resolution. In recent years, many researchers have used event-related potential (ERP) to provide prognosis for patients with consciousness disorders⁵. Evidence-based medical analysis of auditory ERP components (i.e., N100, mismatch negativity and P300) has shown that mismatch negativity (MMN) and P300 are relatively better predictors for patients with low responsiveness in comatose or other conditions⁶. Earlier studies⁷ had focused on the use of electrophysiology to predict consciousness recovery in VS patients after traumatic brain injury. Fischer et al⁸ found that MMN, which is a component of ERP, can be recorded in patients with consciousness disorders. A single salient auditory stimulus interspersed among a series of frequent regular auditory stimuli triggers MMN in the auditory cortex, and it can predict the consciousness recovery in coma patients. Schnakers et al⁹ showed that they were able to record P300 in 6 out of 11 VS patients, which is consistent with previous studies showing that P300 can be elicited in 38% of VS patients. At the same time, it was observed that in MCS patients, P300 latency generated by the patient's own names was longer than in VS patients. It is believed that such replicable ERP wave forms, which are related to recognition and processing, show that patients with traumatic brain injury can execute a certain type of cognitive functions, and that the longer latency of P300 can be used to distinguish VS from MCS. Previous studies showed that the occurrence of MMN and P300 can help determine the prognosis of patients with consciousness disorders^{8, 10-13} since dynamics changes in MMN seem to reflect consciousness recovery in patients with consciousness disorders. As patients recovered a certain level of consciousness, their capability to distinguish auditory stimuli slowly improved, and the abrupt increase in MMN amplitude showed that patients were able to communicate with their environment^{8, 10-13}. Wijnen et al¹² used P3 and MMN to predict functional recovery in 10 patients who were in permanent vegetative state (PVS), and

found that increased MMN amplitude indicated improved consciousness, while ERP assessments showed that patients with a high amplitude and short latency of MMN usually recovered to a relatively higher level of consciousness. Cavinato et al¹⁴ compared the latency and amplitude of N1 and P3 waves in different groups of patients, including 6 patients with PVS and 11 with MCS as well as 10 healthy volunteers, by exposing them to sinusoidal sound waves, their own names, and sinusoidal sound waves with the names of others. Results showed that P3 latency slowly became longer in all the healthy volunteers and patients with MCS as the complexity of auditory stimuli increased, whereas there was no change in patients with PVS. This indicated that prolongation of P3 latency in response to complexity of sound stimuli may represent activity in high-level processing and integration centers, which predicted the transition from VS to MCS in non-conscious patients without corresponding changes in their clinical symptoms. Cavinato et al⁷ conducted follow-up visits, measurements with the disability rating scale, as well as electroencephalograms (EEG), brainstem auditory evoked potentials (BAEP), somatosensory evoked potentials, and P3 assessments of 34 patients with VS within 2-3 months after injury. They found that 26 patients (76%) recovered consciousness, and P3 was the only parameter contributing significantly to prediction of conscious recovery. Fischer et al⁸ found that MMN can be recorded in some patients with PVS or MCS, suggesting that these patients still retained some conscious activity, with the possibility of further recovery. However, these authors did not conduct follow-up visits in their study, thus there was no indication of outcomes for these patients. Lew et al¹³ conducted an auditory ERP study in 22 patients with consciousness disorders after traumatic brain injury, and found that the occurrence of P300 in these patients was linked to a better outcome. Fischer et al¹⁵ conducted an auditory ERP study in 50 coma patients (including patients with brain injury, stroke, and hypoxic-ischemic encephalopathy), and found that the occurrence of P300, but not MMN, was relevant for the determination of patient awakening. Taken together, the results of the analysis of the two above-mentioned component waves show that the occurrence of MMN and P300 is valuable to predict patient awakening.

Because of the large variations in electrophysiology results generated using various paradigms, an increasing number of researchers have

begun to think about the concept of “consciousness”. Consciousness may not be a single concept; instead, it contains multiple functions that are correlated with each other¹⁶. We designed this study based on this idea; therefore, electrophysiological method was used to study patients with consciousness disorders. In addition, clinical follow-ups were conducted for 6 months, in order to investigate the difference between VS and MCS, as well as to assess the correlation between electrophysiological and clinical evaluation results, with the hope of further elucidating the remaining brain function in patients with consciousness disorders.

Patients and Methods

Patients

All patients were hospitalized and diagnosed with consciousness disorders at the Neural Rehabilitation Department in Beijing Boai Hospital between March 2013 and April 2014. Patients selected for this study included six patients with VS (four males and two females; age 26-60 years old) and five patients with MCS (four males and one female; age 18-54 years old).

This study was approved by the appropriate Institutional Review Board, and was in accordance with the Helsinki Declaration on research with human subjects (1975, 2000). Written informed consent was obtained for all participants or their guardians prior to the start of the study.

Patients had to meet the following criteria to be included in the study: (1) A clear history of brain injury; (2) Patients with severe consciousness disorders were required to meet the diagnostic standards of VS or MCS; (3) Disease duration was longer than 3 months, and age was between 18 and 65 years; (4) Patients with impaired auditory nerves were excluded using auditory evoked potentials; (5) No use of drugs (e.g. sedatives) that could affect the study and our observations for at least one week before the study.

Patient presenting the following characteristics were excluded from the study: (1) Patients with hypersomnia, locked-in syndrome, or mental disorders that should be distinguished from VS or MCS; (2) Age less than 18 or more than 65 years; (3) Patients who were unable to complete the assessments included in our study; (4) Patients who had a large area of the skull damaged or missing; (5) Patients who had severe diseases of the heart,

lung, liver, kidney, or other important organs; (6) Patients whose families refused to sign the informed consent forms.

Control Group

Healthy volunteers between 18 and 65 years of age were selected. The group included four males and one female. Age, gender, and education background were matched to the patient groups.

Clinical Data Collection

General Data

Medical history of all participants, including course of disease, was collected by physicians. In addition, we collected relevant demographic and individual characteristics including gender, age, education background, and left/right handedness.

Physical Examination of Neural System

The neural systems of all participants were assessed in detail by physicians to record positive physical characteristics.

Brain Imaging Data and Electrophysiological Examination

All patients underwent computed tomography head scans (GE Healthcare, Little Chalfont, Buckinghamshire, UK) at the start of the study in order to determine the injury site. In addition, brain stem auditory evoked potentials (BAEP) examination was conducted to exclude organic damage to the ear or cochlear nerve, and to ensure that participants were able to hear auditory stimuli.

Treatment

All patients with consciousness disorders received comprehensive rehabilitative treatment including physical therapy for limb and body function, hyperbaric oxygen therapy, and acupuncture.

Clinical Evaluation

The CRS-R (Coma Recovery Scale-Revised) was used to evaluate patients with consciousness disorders in six aspects, including communication, arousal, as well as auditory, visual, motor, and verbal functions according to the previous study¹⁷. The criteria used for the inclusion of patients in the VS or MCS group are presented in Table I.

Table 1. Diagnostic standard for vegetative state and minimally conscious state patients.

CRS-R function	Vegetative state	Minimally conscious state
Auditory	≤ 2	3-4
Visual	≤ 1	2-5
Motor	≤ 2	3-5
Verbal	≤ 2	2
Communication	≤ 0	1
Arousal	N/A	N/A

The CRS-R comprises six functional categories including auditory (score 0-4), visual (score 0-5), motor (score 0-6), verbal (score 0-3), communication (score 0-2), and arousal (score 0-3), with a total score ranging from 0-23. The first five scales were used to distinguish vegetative state (VS) vs. minimally conscious state (MCS) patients, while arousal was not used for diagnosis. Note that to classify a patient as VS all five-measurement score criteria were met, while for MCS the presence of any of the measurement criteria was enough to consider the patient as MCS.

Since error rates for clinical diagnosis in patients with severe consciousness disorders is as high as 40%, two medical practitioners trained for scale evaluation diagnoses the patients in this study, and patients who had consistent diagnoses were ultimately recruited. Activities of patients with severe consciousness disorders were affected by time; therefore, scale evaluation was conducted in patients at four different time points. Patients were evaluated once every 15 days, and ERP examination was conducted if there was any change in the evaluation results at any time. An ERP reexamination was conducted if evaluation results were unchanged for two months.

Examination of Event-Related Potentials

Preparation Before Examination

Participants were asked to wash their hair before examination, and use of any hair oil or conditioner was avoided to prevent wave disappearance or disturbance. Examination was conducted 1 or 2 hours after a meal to avoid the influence of low blood sugar on test results. Researchers tried to ensure that patients were quiet and relaxed.

Equipment and Software

We used an EEG system manufactured by Electrical Geodesics Incorporated (EGI, Nash-

ville, TN, USA). E-prime software (Grand Island, NY, USA) was used to present stimuli, a Net-Station system (San Diego, CA, USA) was used to record evoked potentials, and NetStationv4.3 analysis software (San Diego, CA, USA) was used to analyze ERP data.

Event-Related Potentials Stimulus Array

Participants sat in an electrically shielded and quiet testing room, keeping their body relaxed. In order to complete a task, participants heard a series of continuous sounds interrupted by specific stimuli through double-channel earphones. (1) Pure tone stimuli: frequent stimuli were 1000 Hz, and salient stimuli were 1500 Hz. Both were presented in an oddball paradigm with an 80:20% ratio. Sounds were presented 300 times in total; with duration of 75 ms, bandwidth of 400 Hz, and sound intensity of 90 dB. (2) Name stimuli: subject's own name (SON) and three other first names (OFNs) formed by characters with a similar word frequency to the patient's own name from the Chinese Han character word frequency Table were used. The OFNs could not be the same or similar to the names of the patient's relatives. Four names were presented in an oddball paradigm, with four arrays, 80 words per array (each name was 25%), and a 1300-1400 ms interval between each stimulus. All names were presented using the same female voice with a moderate tone, and the voice intensity was 90 dB.

Electrode Placement and Event-Related Potentials Recording

Patients wore an electrode cap with 128 channels (EGI). Each patient had tasks from two stimuli arrays. MMN was recorded from the pure tone stimuli array, and P300 was recorded from the name stimuli array.

Data Processing and Analysis

Brain electrical signals were continuously collected, with a sample collection rate of 1024 Hz, band-pass filter wave of 0-30 Hz, notch filter of 50 Hz, and scalp resistance maintained at less than 5 K Ω . When recording, bilateral mastoids were used as reference electrodes, and during data analysis their readings were set as the mean value for readings from all electrodes. A level of 100 ms before stimuli presentation was set as baseline, eye movement was set at an amplitude ≥ 60 μ V, eye blinking was set at an amplitude ≥ 200 μ V, and other electromyography artifacts were removed when then mean was taken.

MMN was defined as the maximum negative wave 100-250 ms after stimuli presentation, and P300 was defined as the maximum positive wave 300-600 ms after stimuli presentation. The electrode location with the clearest waveform was set as the point of analysis: Fz point was selected for MMN, and Cz point was selected for P300. The main parameters for analysis were the amplitude and peak value latency period of the various waveforms.

Source localization analysis: The Standardized Low-Resolution Electromagnetic Tomography (sLORETA) method was used for the source localization of evoked potentials on the scalp, which is included in the EGI analysis software package.

Statistical Analysis

Data were analyzed using SPSS v16.0 software (SPSS Inc., Chicago, IL, USA). Quantitative results were presented as mean $\pm$ standard errors, and comparison between groups was done using One-way ANOVA test followed by Least Significant Difference (LSD). In addition, qualitative results were examined using the modified small-sample χ^2 -test. Differences were considered significant when $p < 0.05$.

Results

We summarize in Table II the medical history data collected for patients included in the study, overall CRS-R scores, as well as the results of assessing ERPs and diagnosis determination based on follow-up interviews.

There were no significant differences (t -test, $p > 0.05$) in age of disease onset (41 ± 8.33 vs. 44 ± 5.2), or years of education (9.33 ± 2.78 vs. 9.4 ± 1.68) between the vegetative state (VS) and minimally conscious state (MCS) groups.

Comparison of Mismatched Negativity and P300 Waves in the Three Groups

MMN was elicited in five out of six patients of the VS group, while P300 was elicited in four out of six patients. Both MMN and P300 were elicited in all five patients with MCS, as well as in all five healthy volunteers of the control group. The superimposed averaged waveforms of all groups are shown in Figure 1. The comparison of the amplitudes and latency periods for MMN and P300 for the three groups is shown in Table III.

Table II. Patients' medical history, CRS-R scores, event-related potentials, and diagnosis after follow-up interview.

Patient	Disease	Gender	Age	Education (years)	Disease duration (months)	CRS-R	VS or MCS	Elicited MMV	Elicited P300	Follow-up interview
1	Encephalorrhagia	M	41	16	8	7	VS	Y	Y	MCS
2	Hypoxic-ischemic encephalopathy	F	26	9	11	7	VS	Y	Y	VS
3	Traumatic brain injury	M	45	7	3	6	VS	Y	Y	VS
4	Brainstem infarction	M	60	5	4	6	VS	N	N	VS
5	Encephalorrhagia	M	43	11	5	6	VS	Y	N	MCS
6	Traumatic brain injury	F	31	8	6	7	VS	Y	Y	Awake
7	Encephalorrhagia	M	45	11	7	9	MCS	Y	Y	MCS
8	Hypoxic-ischemic encephalopathy	F	31	8	12	11	MCS	Y	Y	MCS
9	Encephalorrhagia	M	50	9	10	11	MCS	Y	Y	MCS
10	Cerebral infarction	M	48	7	8	9	MCS	Y	Y	Awake
11	Encephalorrhagia	M	46	12	12	13	MCS	Y	Y	MCS

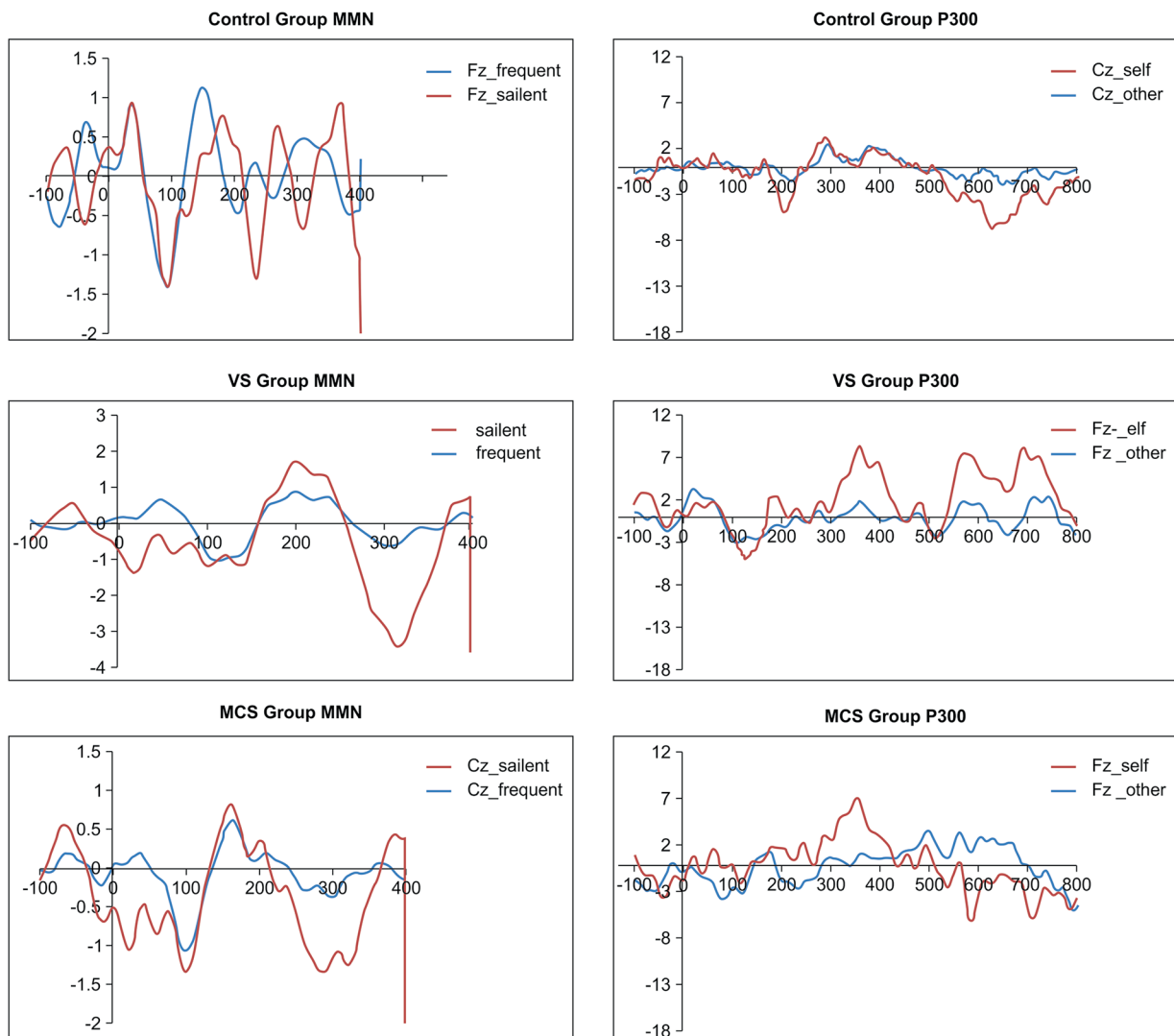


Figure 1. Mismatch negativity and P300 response graphs. Panels on the left present mismatch negativity (MMN) response graphs for the control (upper panel), vegetative state (VS; middle panel), and minimally conscious state (MCS; lower panel) groups. Panels on the right present P300 response graphs for the control (upper panel), VS (middle panel), and MCS (lower panel) groups.

Source Localization Analysis

In the Control Group (Figure 2, upper panel), MMN elicited by salient stimuli was located at -3, 52, -6, with an intensity of 0.010099 nA, at Brodmann area 10 (i.e., middle frontal gyrus of the frontal pole). MMN elicited by frequent stimuli was located at -3, 52, -6, with an intensity of 0.011403 nA, at Brodmann area 10.

In the VS Group (Figure 2, middle panel), MMN elicited by salient stimuli was located at -52, -67, 6, with an intensity of 0.024283 nA, at Brodmann area 19 (i.e., middle temporal gyrus of the occipital pole). MMN elicited by frequent stimuli was located at -59, -39, -20, with an inten-

sity of 0.039062 nA, at Brodmann area 20 (upper inferior temporal gyrus of the temporal pole).

In the MCS Group (Figure 2, lower panel), MMN elicited by salient stimuli was located at 46, 10, -34, with an intensity of 0.070311 nA, at Brodmann area 21 (i.e., middle superior temporal gyrus of the occipital pole). MMN elicited by frequent stimuli was located at -3, -81, 1, with an intensity of 0.066694 nA, at Brodmann area 18 (i.e., lingual gyrus).

In the Control Group (Figure 3, upper panel), P300 elicited by SON was located at -3, 52, -6, with an intensity of 0.037858 nA, at Brodmann area 11 (i.e., middle frontal gyrus of the frontal

Table III. Amplitudes and latency period of mismatched negativity and P300 responses.

Group	N	MISMATCH negativity (Fz)				P300 (Cz)			
		Salient		Frequent		Subjects' own name		Other first names	
		Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)
VS	1	62.25 ^{##} $\pm$ 15.45	1.89 ^{##} $\pm$ 1.26	61.29 $\pm$ 24.32	1.44 $\pm$ 1.15	312.62 ^{##} $\pm$ 72.68	3.25 $\pm$ 1.78	244.00 $\pm$ 21.00	1.57 [#] $\pm$ 1.12
	2	66.13 ^{##} $\pm$ 21.78	1.63 ^{##} $\pm$ 1.05	66.88 $\pm$ 26.36	1.34 $\pm$ 0.77	289.75 ^{##} $\pm$ 67.83	3.26 $\pm$ 1.28	258.24 $\pm$ 43.25	1.49 [#] $\pm$ 1.56
MCS	1	48.00 $\pm$ 9.56	3.74 $\pm$ 1.78	56.24 $\pm$ 27.68	1.15 $\pm$ 1.02	182.56 $\pm$ 75.65	3.39 $\pm$ 1.87	264.76 $\pm$ 68.78	1.68 [#] $\pm$ 1.47
	2	46.50 $\pm$ 7.36	3.34 $\pm$ 1.15	52.63 $\pm$ 32.76	1.72 $\pm$ 1.67	168.78 $\pm$ 89.46	3.445 $\pm$ 1.82	235.94 $\pm$ 95.76	1.82 [#] $\pm$ 1.12
Control		42.50 $\pm$ 15.36	3.42 $\pm$ 2.36	48.86 $\pm$ 28.93	1.39 $\pm$ 1.28	176.65 $\pm$ 76.85	3.65 $\pm$ 2.15	212.34 $\pm$ 112.65	2.45 $\pm$ 1.78

Abbreviations: MCS: minimally conscious state; N: number of times; VS: vegetative state. [#]Indicates a significant difference compared to the control group ($p < 0.05$). ^{*}Indicates a significant difference compared to the MCS group ($p < 0.05$).

pole). P300 elicited by OFNs was located at -3, 52, -6, with an intensity of 0.019716nA, at Brodmann area 10.

In the VS Group (Figure 3, middle panel), P300 elicited by SON was located at -52, -67, 1, with an intensity of 0.093389nA, at Brodmann area 37 (i.e., middle temporal gyrus). P300 elicited by OFNs was located at -52, -67, 1, with an intensity of 0.071744nA, at Brodmann area 37.

In the MCS Group (Figure 3, lower panel), P300 elicited by SON was located at 46, -67, -6, with an intensity of 0.110801nA, at Brodmann area 37 (i.e., lower superior temporal gyrus). P300 elicited by OFNs was located at 4, -81, 1, with an intensity of 0.063377nA, at Brodmann area 18 (i.e., lingual gyrus).

Discussion

Consciousness disorders include three different states: comatose, VS, and MCS¹⁸. In order to improve the diagnostic accuracy of VS and MCS, this study evaluated patients with consciousness disorders using the CRS-R scale at four different time points. Patients were included in the VS or MCS group depending on the results obtained using the CRS-R scales. In addition, a control group composed of healthy volunteers was also included. Pure tone stimuli were used to elicit MMN, while name stimuli were used to elicit P300. MMN occurred in five out of six patients with VS, P300 occurred in four patients, while both MMN and P300 occurred in all patients with MCS. In spite of this, there were no significant differences between the two groups. Previous studies have reported variable results on the occurrence rate of MMN and P300. Similar to our study, Perrin et al¹⁹ used name stimuli (1 SON, 7 OFNs) for their assessment of P300, they found that P300 was elicited in three out of five patients with VS, and in all six patients with MCS. In 2010, Fischer et al⁸ used pure tone (with varied durations) and name (presented by different voices) stimuli to investigate MMN and P300. They found that MMN and P300 were elicited in three out of 11 patients with MCS, and MMN was elicited in two; also, P300 was elicited in three out of 16 patients with VS. Possible reasons for such variability in experimental results include different evaluation methods for consciousness disorders, different course of disease, varied stimuli presentation methods, and varied ERP data analysis methods.

Comparison of Mismatched Negativity and P300 Waves in the Three Groups

In the VS group, MMN amplitude elicited by salient stimuli was significantly lower than in the MCS and control groups, while MMN latency was significantly longer than in the MCS and control groups. The abrupt increase in MMN amplitude and shortened latency by salient stimuli may suggest the recovery of the conscious state, which is consistent with the study by Wijnen et al¹². P300 latency elicited by SON stimuli in the VS group was significantly longer than in the MCS group, suggesting that to a certain extent VS patients were aware of their own names. On the other hand, P300 amplitude elicited by OFNs stimuli in the VS and MCS groups was signifi-

cantly lower than in the control group, indicating that there was a lower awareness for unfamiliar names stemming from the remaining brain function in patients with VS and MCS. Comparison of the MCS and control groups showed that there was a significant difference in P300 amplitude elicited by OFNs stimuli, but no difference for other stimuli. The results above showed that the amplitude and latency of ERP may be valuable to predict the difference between VS and MCS, and to determine whether VS can transition to MCS.

Source Localization Analysis

MMN responses were located in the frontal lobe (Brodmann area 10) in the control group, while they were located in the temporal lobe

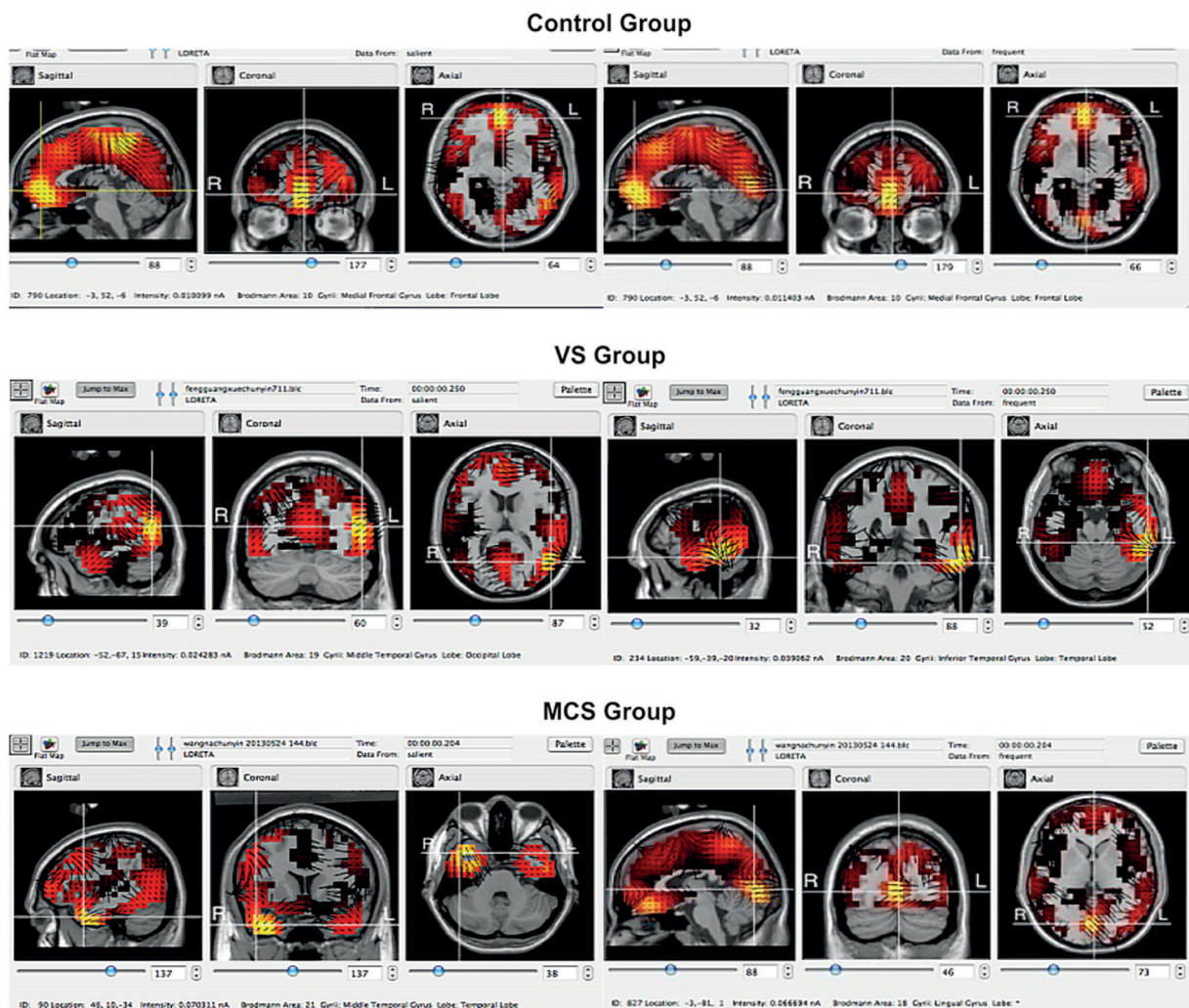


Figure 2. Mismatch negativity brain images. The upper, middle, and lower panels present brain images for the control, vegetative state (VS), and minimally conscious state (MCS) groups, respectively. For each group, sagittal, coronal and axial images are presented (left, mid, and right, respectively).

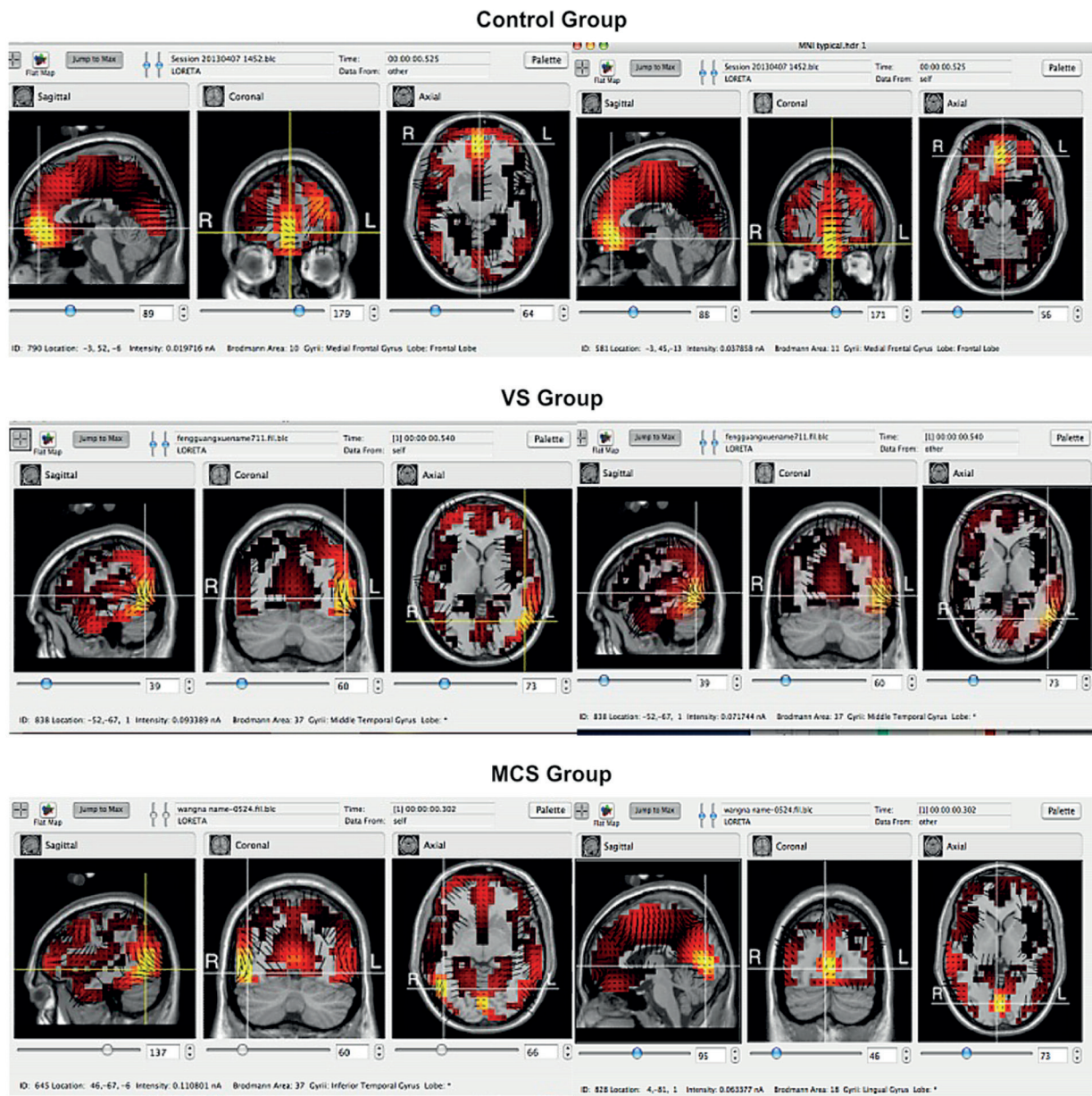


Figure 3. P300 response brain images. The upper, middle, and lower panels present brain images for the control, vegetative state (VS), and minimally conscious state (MCS) groups, respectively. For each group, sagittal, coronal and axial images are presented (left, mid, and right, respectively).

in the VS (Brodmann area 19 or 20) and MCS groups (Brodmann area 18 or 21). P300 in the control group was mainly located in the frontal lobe (Brodmann area 10 or 11), while in VS and MCS groups it was located in the temporal lobe (Brodmann area 18 or 37). The source for MCS was mainly located in the superior temporal and middle temporal gyri (i.e., closer to the higher-level cortices of the frontal lobe), while the source for VS was mainly located in the middle

and inferior temporal gyri. Despite there was no significant difference in the amplitude and latency between MCS and control groups, the source location in the MCS group (i.e., the temporal lobe) was clearly different from the control group, which is likely the reason why MCS patients have better clinical responses than VS patients. Although they were still not fully awake, and remained as MCS clinically. Therefore, although VS and MCS had poorer responses to the envi-

ronment, they still presented various levels of awareness responses, which were mostly located at the level of the auditory cortex.

Patient's Follow-up and Effect of Treatment on Mismatched Negativity and P300 Responses

In this work, no significant differences were found between MCS and VS groups pre-and post-treatment, which was likely related to the fact that the selected patients were mostly in recovery, and the time of follow-up visit was relatively short.

Furthermore, we interviewed all patients (or their families) over the phone after six months. Among the four patients in the VS group who presented MMN and P300 responses, two were still VS, one was awake, and the other transitioned to MCS. Noteworthy, the patient who presented MMN responses (but not P300) had transitioned to MCS, while the patient who did not respond to MMN or P300 was still VS. In the MCS group, where all five patients presented MMN and P300 responses, two were awake at the time of follow-up interview, while the other three were still MCS. One of the patients awoke 1 month after leaving the hospital, and after reviewing the ERP results of this patient, we found that the MMN before leaving the hospital also showed a trend with high amplitude and short latency, consistent with the above-mentioned conclusion. The other patient awoke four months after leaving the hospital, although no similar MMN could be observed in this patient. This may be because a long time passed between ERP and the time the patient awoke; therefore, this result was not recorded. This suggests that there may be a specific time window for the change in ERP results. More continuous clinical monitoring will be needed to further understand similar cases.

Based on the results of ERP amplitudes and latency of this study, the abrupt changes of amplitude and latency in patients may be valuable to predict changes in consciousness state; however, there was no enhanced ERP amplitude or prolonged latency as the CRS score improved, suggesting that there is limited value for the amplitude and latency of MMN and P300 to predict or distinguish between VS and MCS. Variations in the source localization of MMN may show that although MMN can be elicited when patients were not paying attention, MMN generated from healthy volunteers requires an attentive state, as well as other high-level cog-

nitive processes, which are mainly located in the frontal lobes. While MMN and P300 in VS are mainly located in the sensory cortex of the temporal lobes, which suggests that processing of auditory stimuli in patients was primarily focused in the auditory cortex, further processing of the information was limited, which may be the primary reason why these patients failed to respond well to the external environment. The results of the four ERP examinations performed supported this view. MCS patients had better clinical responses than VS patients, and their source localization was closer to higher-level cortices in the frontal lobes.

Conclusions

We believe that there is limited value for MMN and P300 responses as predictors of the recovery of conscious state, although the abrupt changes of amplitude and latency may have some relevance for the change of conscious state. Source localization may be more persuasive evidence to determine conscious state, and may be valuable to distinguishing and diagnose VS and MCS. Our study had a relatively small sample size, and the follow-up interview period was relatively short, while patients had a relatively long course of disease of at least three months, and their recovery was relatively slow. Therefore, clinical studies with larger sample sizes and long-term clinical follow-ups will be needed to verify this view, which will be our next research focus. Moreover, the recovery from consciousness disorders is related to many factors in the patients, including cause of disease, age, degree of pathological changes, course of disease, which should be considered in future research.

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Authors' Contributions

ZH and ZT participated in the design of the study, WXY participated in the design of the study, carried out experiments, wrote the manuscript; WHY analyzed experimental results; LHT and HTT conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

No conflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication.

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