OPEN

Assessing consciousness with auditory event-related potential during coma recovery: a case study

Xiaoyan Wang, Hao Zhang, Xiaonian Zhang, Xinting Sun and Tong Zhang

To observe changes in mismatch negativity (MMN) and P300 in a patient transitioning from a vegetative state (VS) to a minimally conscious state (MCS). One patient with intracerebral hemorrhage and an 8-month disease course was evaluated as being in the VS using the Coma Recovery Scale-Revised. Two weeks after the patient was admitted to the hospital, another evaluation was performed, and the patient was determined to be in an MCS. Using the Oddball paradigm, pure tone and name stimuli were presented to the patient to study event-related potentials (ERPs). A 15-week clinical follow-up was carried out, and four ERP examinations were performed at 2 days and 2, 6, and 15 weeks after admission. One healthy individual was assessed as a control participant. MMN and P300 were elicited in all four ERP examinations. MMN and P300 may occur earlier than believed in patients in persistent VS and MCS; their predictive values for prognosis need to be further confirmed by follow-up studies on a large clinical sample. *NeuroReport* **26:50–56**

NeuroReport 2015, **26**:50–56

Keywords: Coma Recovery Scale-Revised, event-related potential, minimally conscious state, vegetative state

Rehabilitation Medicine College of Capital Medical University, Chinese Rehabilitation Research Center, The Beijing Boai Hospital, Beijing City, China

Correspondence to Tong Zhang, Rehabilitation Medicine College of Capital Medical University, Chinese Rehabilitation Research Center, The Beijing Boai Hospital, 10, Jiaomen North Street, FengTai District, Beijing City 100068, China
Tel: +86 137 013 95941; fax: +86 010 675 73428;
e-mail: wxy-770328@126.com

Received 2 July 2014 **accepted** 7 October 2014

Introduction

Disorders of consciousness commonly occur in patients with severe brain injury. The most common disorders of consciousness include vegetative state (VS) and minimally conscious state (MCS). Patients in MCS show weak but definite self-awareness or environmental awareness, and some patients have spontaneous eye opening and sleep–wake cycles. Although the patient's cognitive behaviors are intermittent, they are reproducible or can last long enough to be distinguished from primitive reflexive activity [1,2]. A patient in MCS is clearly distinguishable from a VS patient. Although MCS patients remain unable to communicate, the behavioral evidence of self-awareness and environmental awareness is clear. A VS or an MCS may be prolonged and can continue until the patient's death [3]. Currently, consciousness assessments mainly rely on clinical signs and various scales. The Coma Recovery Scale-Revised (CRS-R) is an internationally recognized scale for assessing VS [4]. It evaluates auditory, visual, sensory, motor, and communicative responses and can sensitively reflect changes in patients' conditions. Therefore, the CRS-R has become the primary method to diagnose MCS in clinical trials and in follow-up and evaluation. However, clinical scales are very subjective and do not accurately identify small changes in consciousness. Electrophysiological examinations have certain advantages for the evaluation of patients with consciousness disorders because of their objectivity and high temporal resolution. Many studies have used event-related potential (ERP) to assess prognoses of patients with consciousness disorders. Mismatch negativity (MMN) is a negative component appearing in the primary auditory and prefrontal cortices [5] around 100–250 ms after any auditory change in a monotonous sequence of sounds (i.e. an oddball paradigm AAAB) [6]. The low amplitude of MMN implies that many repetitions are needed to observe a response. The MMN is elicited by deviants generated by automatic change detection processes that occur when the current auditory input is different from the preceding one. Deviants can be detected if patients are not aware of the auditory changes, provided the changes exceed the patient's discrimination threshold [7]. MMN is even evoked when the patients focus attention on aspects other than the auditory stimuli [8,9]. Thus, this makes ERP assessment in coma patients very interesting. The P300 is a positive component generated when patients detect a rare and unexpected stimulus in a regular train of standard stimuli (i.e. oddball paradigm) [10]. MMN and P300 are two different brain responses elicited by similar stimuli (deviant or novel), and their latencies after stimuli are different. For an auditory potential, P300 appears around 300 ms after stimulus presentation, but for a visual potential, it may appear after 500 or 600 ms. The P300 corresponds to activation of a frontoparietal network [11]. In such paradigms, a P300 wave might reflect either recognition of the target's intrinsic meaning or detection of its acoustic salience. Many authors have investigated

DOI: 10.1097/WNR.0000000000000288

MMN and P300 in comatose patients, but with inconclusive results [12–17]. One evidence-based medical analysis on the predictive values of N100, MMN, and P300 (auditory EPR components) found that MMN and P300 had greater predictive value in comatose and other low-response patients [18]. However, it is unclear whether auditory ERP can be measured during recovery from coma and whether it can be used to measure sensitive changes in consciousness. Moreover, most of these studies assessed patients in the acute stage; patients in the recovery phase of coma were rarely studied. Few clinical studies have observed how these ERPs change or examined the long-term predictive value of MMN and P300 in prognosis. The present study was designed to focus on these issues.

Here, we performed a 15-week clinical follow-up on a 42-year-old man with intracerebral hemorrhage with persistent VS for 8 months. During admission, the patient showed a sleep–wake cycle and flexor responses in the limbs to supraorbital pressure, but did not respond to sound and light stimulation. Every 2 weeks, the patient was scored with the CRS-R by two specialists. ERP examinations were performed at 2 days and 2, 6, and 15 weeks after admission. The corresponding CRS-R scores were 7/23, 9/23, 11/23, and 11/23, respectively.

Methods

Before the experiment, brainstem auditory evoked potential testing was performed to exclude hearing impairment. The patient was also scored with the CRS-R before each examination.

The experiment was approved by the Ethics Committee of the Faculty of Medicine of the hospital. Written informed consent was obtained from a member of the patient's family and from control participants.

Auditory ERP recording (MMN)

Auditory stimuli were delivered binaurally through inserted earphones at an intensity of 90 dB HL using the Presentation software (E-prime software, Electrical Geodesics Inc., Eugene, Orlando, USA). The oddball stimulation paradigm with pure tones lasted 75 ms and included frequent tones (1000 Hz) and salient tones (1500 Hz). The two tones selected for the acoustic test were determined as 20 and 80% of the 400 Hz bandwidth range. The patients heard the tones with their headphones and responded.

P300

We elaborated four sequences of 80 stimulations comprising four first names, with one of them always being the subject's own name (SON). The three other first names (OFNs) were selected from Chinese character tables as a series of first names with similar high frequencies. For each sequence, each name was presented 10 times randomly, thus making a complete series of 80 equiprobable first names (25% probability for each name), with an interstimulus interval between 1300 and 1400 ms. After each recording session, the patient or their family was asked whether any of the other names had particular emotional importance (e.g. they corresponded to names of close relatives or friends). If yes, the name was excluded from the ERP analysis. All first names were recorded by the same neutral female voice (FP), and were digitized and replayed binaurally at a 90 dB sound pressure level maximal intensity.

Electrophysiological data acquisition and analysis

The E-prime software was used to present the stimuli, and electroencephalography (EEG) activity was continuously recorded and analyzed with Netstation 4.3. The data obtained from 128 scalp electrodes mounted on an elastic cap (Electrical Geodesics Inc., Riverfront Research Park, Eugene, Orlando, USA) were bandpass filtered at 3–30 Hz, notched at 50 Hz, and digitized at a sampling rate of 1024 Hz. Skin/electrode impedance was maintained below 5 kΩ. All scalp signals were referenced online to both mastoids, but were later offline rereferenced to the average of all scalp electrodes. Trials were averaged to ERPs separately for each condition and each patient relative to a 100 ms prestimulus baseline. Single epochs with an amplitude of at least 60 μV or those containing eye movements and epochs with an amplitude of at least 200 μV because of eye blinking or electromyographic artifacts were excluded from averaging.

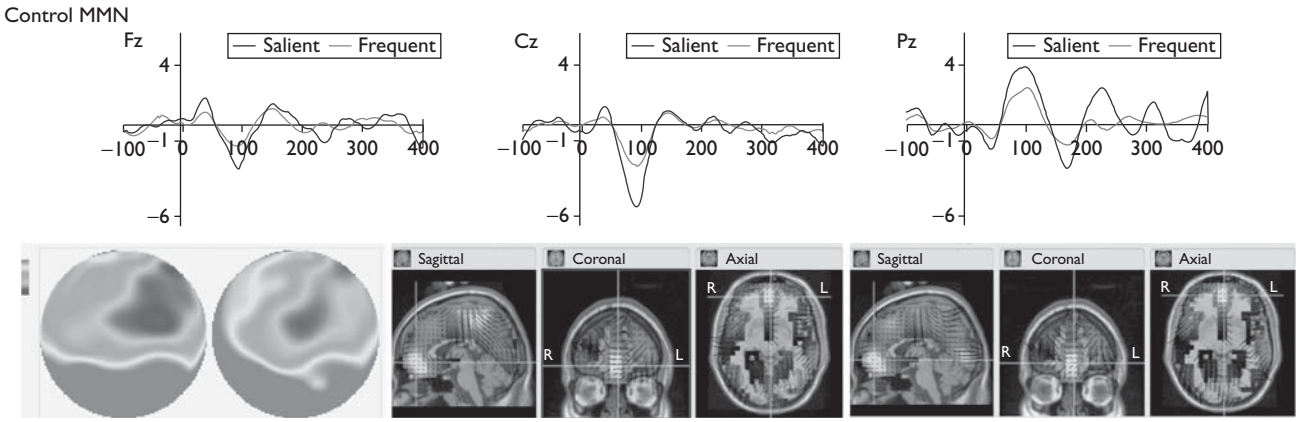
Source localization results

We used standardized low-resolution electromagnetic tomography (sLORETA) [19] to provide estimates of the cortical sources of the evoked potentials. The LORETA solution was included in the EGI analysis package (Geosource, Electrical Geodesics Inc., Eugene, Orlando, USA). LORETA relies on physiological theories to add constraints to depth weighting. This scheme selects the solution with the smoothest spatial distribution. LORETA was used to compute 3D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model, including the scalp, skull, and brain compartments. A voxel was labeled as gray matter if its probability of being gray matter exceeded 33%, exceeded the probability of being white matter, and exceeded the probability of being cerebrospinal fluid. In the current implementation, a spatial resolution of 7 mm is used, producing 2394 voxels.

Results and discussion

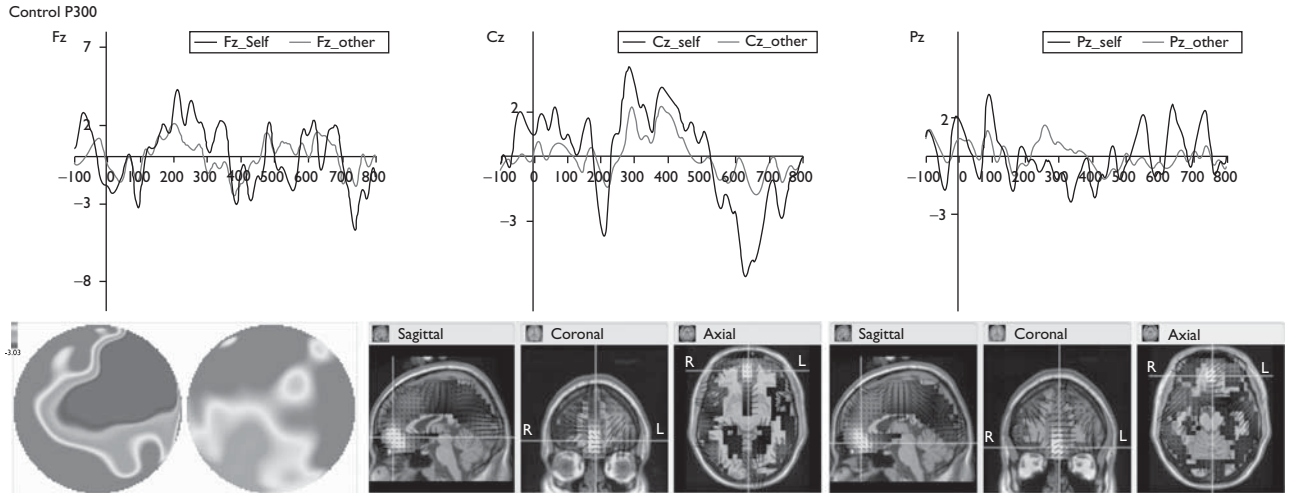
Figures 1 and 2 show the MMN and P300 in the normal control participants. The salient tone-induced MMN (red line, negative wave between 100 and 200 ms) location was −3, 52, −6; intensity: 0.01099 nA; Brodmann area: 10; gyri: medial frontal gyrus in the frontal lobe. The frequent tone (blue line) was the same, except that the intensity was 0.011403 nA. The SON-induced P300 (red

Fig. 1



ERPs to pure tone in the normal control participant. EEG waveforms and the cortical sources of the MMN are shown. EEG, electroencephalography; ERP, event-related potential; MMN, mismatch negativity.

Fig. 2



ERPs to name in the normal control participant. EEG waveforms and the cortical sources of the P300 component are shown. EEG, electroencephalography; ERP, event-related potential.

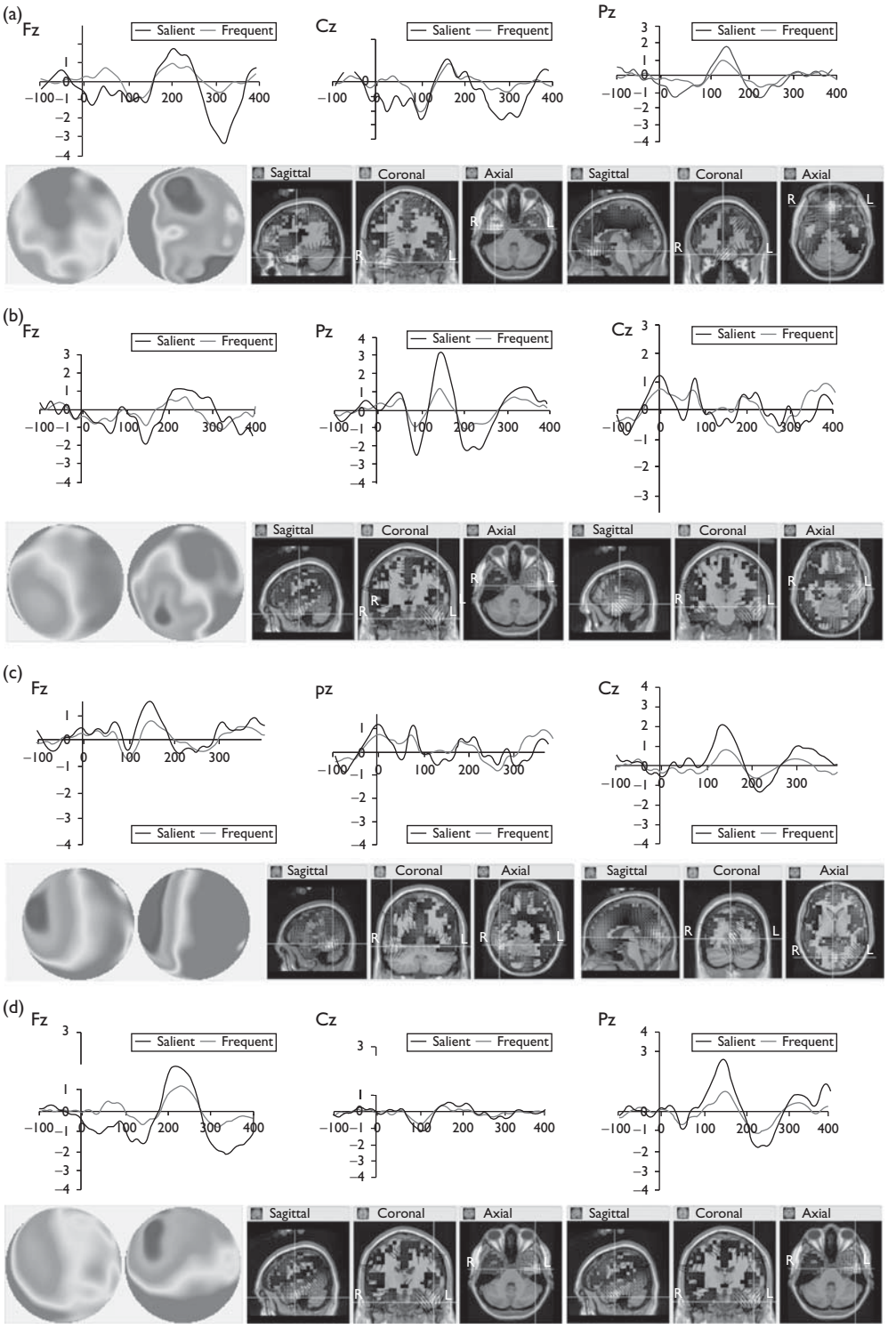
line, positive wave around 300 ms) location was − 3, 45, − 13; intensity: 0.037858 nA; Brodmann area: 11; gyrus: medial frontal gyrus in the frontal lobe. The OFNs (blue line, positive wave around 300 ms) elicited a response at − 3, 52, − 6; intensity: 0.019716 nA; Brodmann area: 10; gyrus: medial frontal gyrus in the frontal lobe.

Figures 3 and 4 show the patient's evoked potentials. The locations are the frontal and temporal lobes. Table 1 lists the latencies and amplitudes of detected MMNs and P300s.

The MMN amplitudes evoked by salient stimuli were higher than those evoked by frequent stimuli, whereas the latencies of the former were shorter than those of the latter. The SON-evoked P300 amplitudes were higher than those evoked by OFNs. When the CRS-R score indicated VS, the latencies of P300 evoked by SONs were longer than those evoked by OFNs. However, when the CRS-R score indicated an MCS, the latencies of P300 evoked by SONs were shorter than those evoked by OFNs.

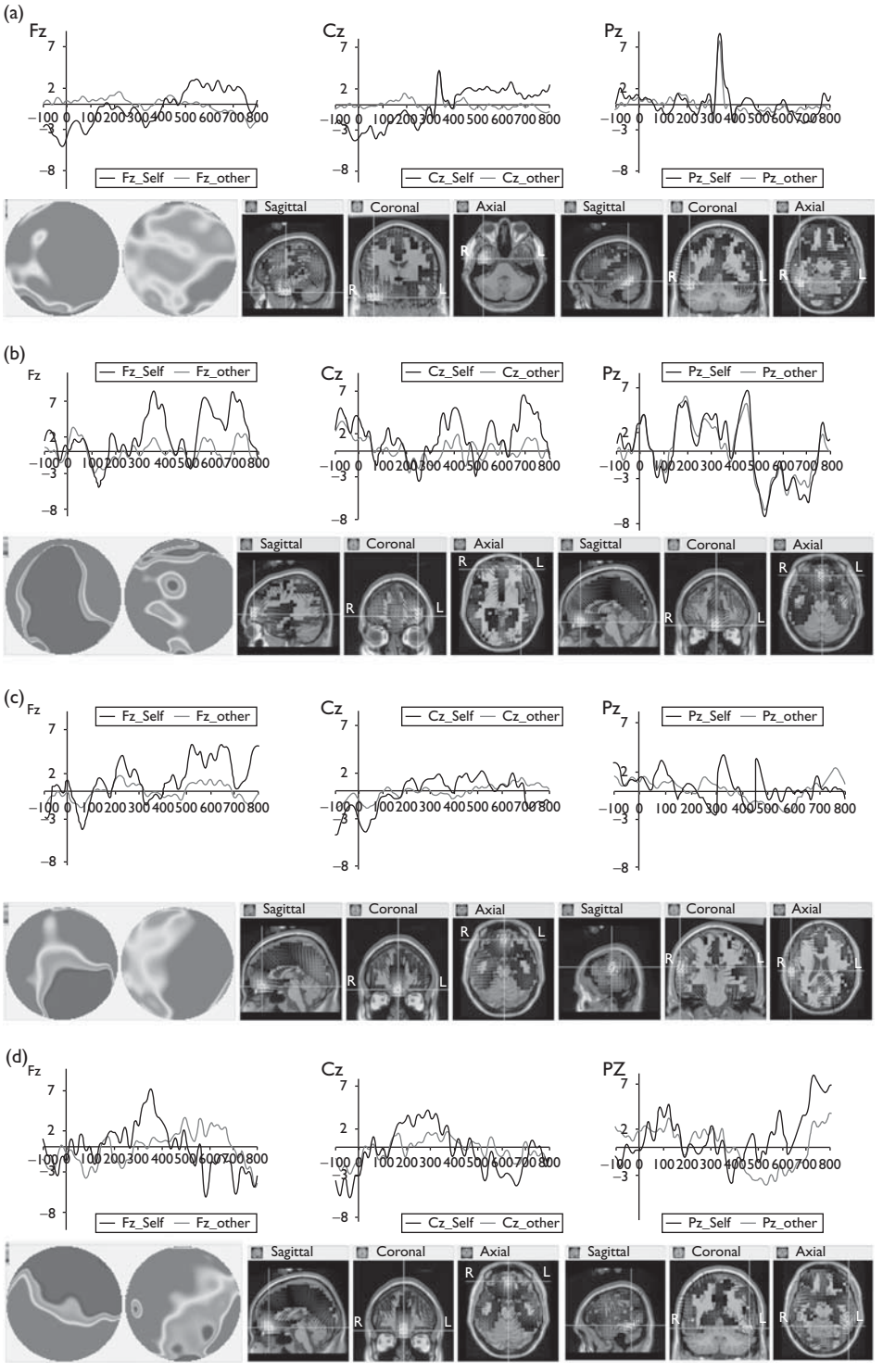
For the control participant, MMN amplitudes and latencies evoked by salient and frequent stimuli were roughly the same. The SON-evoked P300 amplitude was higher than that evoked by OFN, and the SON-evoked P300 latency was shorter than that evoked by OFN. In addition, while studying ERP, we carried out topographic EEG and source analysis. The results showed that MMN

Fig. 3



ERPs to pure tone in the patient during each of the four assessments (a–d). (a) Patient MMN. ERP was first performed 2 days after admission when the patient was in a VS; the CRS-R score was 7/23. (b) ERP was again performed 2 weeks after admission; the patient was in an MCS with a CRS-R score of 9/23. (c) ERP was again performed 6 weeks after admission; the patient was in an MCS with a CRS-R score of 11/23. (d) ERP was again performed 15 weeks after admission; the patient was in an MCS with a CRS-R score of 11/23. CRS-R, Coma Recovery Scale-Revised; ERP, event-related potential; MCS, minimally conscious state; MMN, mismatch negativity; VS, vegetative state.

Fig. 4



The patient's ERPs to names during each of the four assessments (a–d). (a) P300 in the first ERP assessment 2 days after admission; the patient was in a VS and had a CRS-R score of 7/23. (b) ERP was performed 2 weeks after admission; the patient was in an MCS and had a CRS-R score of 9/23. (c) ERP was performed 6 weeks after admission; the patient was in an MCS and had a CRS-R score of 11/23. (d). ERP was performed 15 weeks after admission; the patient was in an MCS and had a CRS-R score of 11/23. CRS-R, Coma Recovery Scale-Revised; ERP, event-related potential; MCS, minimally conscious state; VS, vegetative state.

Table 1 Latencies and amplitudes of individually detected waves

			MMN (Fz)				P300 (Cz)			
			Salient		Frequent		SON		OFN	
	Time	CRS	Latency (ms)	Amplitude (μv)	Latency (ms)	Amplitude (μv)	Latency (ms)	Amplitude (μv)	Latency (ms)	Amplitude (μv)
Patient	1	7	18	−1.499	110	−1.014	536	3.173	236	1.144
	2	9	144	−1.031	144	−0.842	248	4.117	312	1.932
	3	11	52	−0.740	106	−0.151	324	2.170	584	1.378
	4	11	54	−1.317	142	−0.672	96	4.447	272	1.824
Control			90	−1.423	90	−1.394	172	2.835	192	2.301

MMN were measured at Fz. P300 was measured at Cz.
CRS-R, Coma Recovery Scale-Revised; MMN, mismatch negativity; OFN, other first names; SON, subject's own name.

was generated in the frontal and temporal lobes and that P300 was generated in the frontal, temporal, and parietal lobes. This was consistent with previous studies [20].

The occurrences of MMN and P300 are indicative of a good prognosis in patients with consciousness disorders [14,21–23]. Along with increasing recovery of consciousness in these patients, there was a gradual increase in their ability to distinguish auditory stimuli. A sudden increase in MMN amplitude suggested that the patients could interact with their environment. Fischer *et al.* [14] found that MMN could still be recorded in some patients in permanent VS or MCS, indicating some level of awareness in these patients and the possibility of further recovery. However, they did not carry out a follow-up study or describe the outcomes of these patients. Lew *et al.* [23] carried out an auditory ERP study on 22 patients with disorders of consciousness caused by severe traumatic brain injury (TBI) and claimed that the occurrence of P300 in these patients indicated better patient outcome. Cavinato *et al.* [24] carried out an auditory ERP study in 34 patients in a 2–3-month VS following TBI. The auditory stimuli were 1000 Hz pure tones and SONs, and they found that the conscious states of the patients in whom P300 was recorded were improved at the 1-year follow-up. Fischer *et al.* [25] carried out an auditory ERP study in 50 comatose patients (including patients with TBI, stroke, and hypoxic-ischemic encephalopathy) and found that the emergence of MMN could not predict whether patients would regain consciousness. Conversely, their results indicated that P300 emergence played a predictive role in determining whether the patients would regain consciousness. Taken together, the experimental results implied that the presence of P300 could predict whether patients would regain full consciousness.

In the present study, an auditory ERP study was carried out on one patient in a persistent VS (CRS-R7/23) using pure tone and name stimuli, while MMN and P300 were simultaneously recorded. The patient was evaluated by CRS-R at 2 and 6 weeks after his first ERP examination. Interestingly, the patient's CRS-R scores increased (CRS-R 9/23 and 11/23), and intermittent verbal communication appeared. After 15 weeks, the patient's CRS-R scores stabilized, and another ERP examination was performed. According to the first assessment after he was admitted, the patient was in a VS because of an intracerebral hemorrhage. The disease course was up to 8 months; thus, the patient should have been diagnosed as being in a persistent VS (>6 months). However, MMN and P300 were recorded simultaneously during ERP examinations, suggesting that the patient might still recover. At 2 weeks after admission, the patient's consciousness state actually improved, indicating that MMN and P300 might occur earlier than improvements on clinical assessments of behavior; however, this hypothesis needs to be tested in a large sample. However, the MMN and P300 amplitudes did not increase with the improved state of consciousness (Table 1). In addition, the patient's consciousness state did not show significant recovery from 6 to 15 weeks after admission. Although the ERP examination showed MMN and P300 at all ERP examinations, the consciousness state of the patient has not yet significantly improved at 15 months, which may indicate that MMN and P300 can be recorded in patients in permanent VS or MCS, indicating some level of awareness and possibility of further recovery. This is in agreement with the study of Fischer *et al.* [13]. Therefore, the predictive value of MMN and P300 for consciousness recovery needs to be explored in a large sample and with a long-term clinical follow-up.

On the basis of our results, we can conclude that MMN was generated in the frontal and temporal lobes, whereas P300 was generated in the frontal, temporal, and parietal lobes. MMN and P300 might emerge earlier than previously believed and continue in persistent VS and MCS. The predictive value of these ERPs for subsequent recovery of consciousness should be studied in a large sample with long-term clinical follow-up. Our group will continue this study and carry out a long-term clinical follow-up to find the predictive value of these ERPs.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Wang M, O'Young BJ, Ward CD. *Neurorehabilitation*. Beijing, China: People's Medical Publishing House Co. Ltd; 2009. pp. 613–615.
2 Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, *et al*. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58**:349–353.
3 Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 2011; **258**:1373–1384.
4 Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, *et al*. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009; **9**:35.
5 Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hear* 1995; **16**:38–51.
6 Näätänen R, Lehtokoski A, Lennes M, Cheour M, Huotilainen M, Iivonen A, *et al*. Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature* 1997; **385**:432–434.
7 Sams M, Paavilainen P, Alho K, Näätänen R. Auditory frequency discrimination and event-related potentials. *Electroencephalogr Clin Neurophysiol* 1985; **62**:437–448.
8 Näätänen R, Kujala T, Winkler I. Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. *Psychophysiology* 2011; **48**:4–22.
9 Näätänen R. Mismatch negativity (MMN) as an index of central auditory system plasticity. *Int J Audiol* 2008; **47 (Suppl 2)**:S16–S20.
10 Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. *Science* 1965; **150**:1187–1188.
11 Pegado F, Bekinschtein T, Chausson N, Dehaene S, Cohen L, Naccache L. Probing the lifetimes of auditory novelty detection processes. *Neuropsychologia* 2010; **48**:3145–3154.
12 Rodriguez RA, Bussière M, Froeschl M, Nathan HJ. Auditory-evoked potentials during coma: do they improve our prediction of awakening in comatose patients? *J Crit Care* 2014; **29**:93–100.
13 Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol* 1999; **110**:1601–1610.
14 Fischer C, Luaute J, Morlet D. Event-related potentials (MMN and novelty P3) in permanent vegetative or minimally conscious states. *Clin Neurophysiol* 2010; **121**:1032–1042.
15 Lehembre R, Gosseries O, Lugo Z, Jedidi Z, Chatelle C, Sadzot B, *et al*. Electrophysiological investigations of brain function in coma, vegetative and minimally conscious patients. *Arch Ital Biol* 2012; **150 (2–3)**:122–139.
16 Faugeras F, Rohaut B, Weiss N, Bekinschtein TA, Galanaud D, Puybasset L, *et al*. Probing consciousness with event-related potentials in the vegetative state. *Neurology* 2011; **77**:264–268.
17 Perrin F, Schnakers C, Schabus M, Degueldre C, Goldman S, Brédart S, *et al*. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Arch Neurol* 2006; **63**:562–569.
18 Daltrozzo J, Wioland N, Mutschler V, Kotchoubey B. Predicting coma and other low responsive patients outcome using event-related brain potentials: a meta-analysis. *Clin Neurophysiol* 2007; **118**:606–614.
19 Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol* 2002; **24 (Suppl D)**:5–12.
20 Zhang R, Song W. The application of auditory event-related potentials in the evaluation of disorders of consciousness. *Chinese J Rehabil Med* 2012; **27**:1178–1182.
21 Qin P, Di H, Yan X, Yu S, Yu D, Laureys S, *et al*. Mismatch negativity to the patient's own name in chronic disorders of consciousness. *Neurosci Lett* 2008; **448**:24–28.
22 Wijnen VJ, van Boxtel GJ, Eilander HJ, de Gelder B. Mismatch negativity predicts recovery from the vegetative state. *Clin Neurophysiol* 2007; **118**:597–605.
23 Lew HL, Dikmen S, Slimp J, Temkin N, Lee EH, Newell D, Robinson LR. Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. *Am J Phys Med Rehabil* 2003; **82**:53–61.
24 Cavinato M, Freo U, Ori C, Zorzi M, Tonin P, Piccione F, Merico A. Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. *Brain Inj* 2009; **23**:973–980.
25 Fischer C, Dailler F, Morlet D. Novelty P3 elicited by the subject's own name in comatose patients. *Clin Neurophysiol* 2008; **119**:2224–2230.