Assessing consciousness with auditory event-related potential during coma recovery: a case study
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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 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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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
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 ERP 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 ERP s 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; gyr: 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
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
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.
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.
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-

### Table 1 Latencies and amplitudes of individually detected waves

| Time | CRS | Salient MMN (Fz) | Frequent MMN (Fz) | Frequent P300 (Cz) | Salient P300 (Cz) | Control |
|------|-----|----------------|----------------|-------------------|----------------|---------|
|      |     | Latency (ms)  | Amplitude (μv) | Latency (ms)  | Amplitude (μv) | Latency (ms)  | Amplitude (μv) | Latency (ms)  | Amplitude (μv) | Latency (ms)  | Amplitude (μv) |
| 1    | 7   | 18              | -1.499          |        | -0.104          | 436        | 3.173          | 236          | 1.144 |
| 2    | 9   | 144             | -1.031          | 144    | -0.842          | 248        | 4.117          | 312          | 1.932 |
| 3    | 11  | 50              | -0.760          | 106    | -0.151          | 324        | 2.170          | 594          | 1.378 |
| 4    | 11  | 54              | -1.317          | 142    | -0.672          | 96         | 4.447          | 272          | 1.824 |
| 5    | 11  | 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.

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.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.
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