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Changes in Event-Related Potentials Underlying Coma Recovery in Patients with Large Left Hemispheric Infarction

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Background: The aim of this study was to investigate changes in event-related potentials (ERPs) between coma and awakening in patients with large left hemispheric infarction (left LHI).

Material/Methods: Ten patients with left LHI who suffered coma and survived to awaken were enrolled in this study. The eye-opening subscore of the Glasgow Coma Scale (GCS) was used to assess the extent of patients' arousal. ERPs elicited by the passive oddball paradigm were collected during coma and awakening states, respectively. Peak latencies, peak amplitudes, topography, and time-frequency information of P1, N1, P2, and mismatch negativity (MMN) were compared between the 2 sessions.

Results: No significant differences in the peak amplitudes and peak latencies of P1 and N1, but significantly greater P2 amplitude with shorter latency in left hemisphere and midline was shown in the awakening state compared with that in coma. A marked shift of P2 topography in response to deviant tones was also seen, from the right centro-parieto-frontal areas during coma to left frontal-midline areas during awakening. MMN waveforms were not detected in 6/10 patients during the coma state, but these 6 patients all recovered to awakening. Evoked oscillations in bilateral hemisphere were profoundly inhibited during the coma state, with poor inter-trial phase synchronization, while obvious activities with broader frequency ranges and consistent inter-trial phase synchronization were observed during awakening state, and different frequency activities were distributed in distinct brain regions.

Conclusions: P2 may be a central index of coma recovery and a component of the arousal system. Changes in time-frequency information could provide more information during coma recovery, perhaps including some cognitive processing of the sensory stimulus.

MeSH Keywords: Cerebral Infarction • Coma • Consciousness • Evoked Potentials

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Background

Consciousness can be divided into two components: arousal and awareness. The traditional view has been that arousal is maintained by the ascending reticular activating system in the brainstem and thalamus, whereas awareness depends on extensive cortico-cortical connectivity. To date, most studies on disorders of consciousness (DoC) have focused on the chronic stage of DoC, such as the vegetative state (VS) and minimally conscious state (MCS), during which awareness is the vital problem.

Studies on VS and MCS, mainly based on functional neuroimaging techniques, have focused on awareness or cognition [1–5]. However, for awareness or cognitive performance, the brain must be highly aroused. As one aspect of consciousness, albeit an indispensable one, awakening was considered entirely distinct from awareness, but these 2 processes are sometimes blended together and difficult to separate. Therefore, it is important to pay attention to awakening, and precise knowledge of the mechanisms underlying awareness is required. Awakening is the basis of awareness recovery. Recently, there have been many studies on coma, but they focused on prediction of coma recovery [6–10]. There are few studies reporting the neurophysiological mechanisms or ERP changes related to coma and awakening.

Regarding the mechanisms of coma recovery, the traditional theory supports the projection of the ascending reticular activating system in the brainstem and thalamus into the entire cerebral cortex. Awakening from a coma might be more complex than previously assumed by the anatomical model. Valatx [11] described the mechanism of awakening from anatomical and physiological perspectives and suggested that awakening is produced and maintained by a complex network composed of at least 10 neuron groups. However, knowledge of the processes and mechanisms of awakening remains limited.

Functional neuroimaging techniques are not feasible for critical patients in the acute stage of coma. Neurophysiological techniques are noninvasive, simple, and can provide continuous evaluation of brain function at bedside; they are especially suitable for critically comatose patients. Event-related potentials (ERPs) are long latency potentials generated by subcortico-cortical and cortico-cortical loops, which depend on more cortical and extensive neural connections. They have a certain significance for the detection of the integrity of cortical and subcortical functions, and are more suitable for the study of consciousness.

As the most extensively studied component, P3 is considered as an endogenous component related to cognition or awareness. Traditionally, P1, N1, P2, and MMN were considered as exogenous components associated with primary processing of sensory stimuli. Since endogenous components reflect awareness, do exogenous components reflect the awakening function? Few studies have addressed the relationship between awakening and the exogeneous ERP components. We hypothesized that P1, N1, P2, and MMN are related to awakening, and neurophysiological changes may occur that are not localized in one region or a unilateral area, but rather in the whole brain. Exploring the neurophysiological changes underlying coma recovery would further elucidate the awakening process and might provide evidence for the selection of stimulation targets for wake-promotion therapy during the acute coma stage.

The present prospective longitudinal study was conducted to explore changes in patterns of P1, N1, P2, and MMN in response to a passive oddball paradigm in terms of latency, amplitude, topography, and time-frequency information and their associations with awakening.

Material and Methods

Participants

Ten eligible patients with large left hemispheric infarction admitted to Xuanwu Hospital, Capital Medical University, Beijing, China from June 2017 to December 2018 were prospectively and consecutively enrolled in this study. We considered that the ERPs may be affected in different patterns in patients with left and right LHI patients. To ensure the consistency of subjects, we only included patients with left LHI, and right LHI patients will be included in a future study. Patients were eligible if they satisfied the following criteria: (i) left large hemispheric infarction with the volume at least 2/3 territory of the left middle cerebral artery determined neuroradiologically by computed tomography (CT) or magnetic resonance imaging (MRI); (ii) first ever infarction in acute stage; (iii) age 18–80 years; (iv) patients who suffered coma (the eye-opening subscore of GCS is 1, E1) during the edema peak. The exclusion criteria were: (i) decompressive craniectomy after coma; (ii) death or removal from further therapy before awakening (the eye-opening subscore of GCS is 4, E4); (iii) patients who had neuropsychiatric disorders in the past; (iv) infarction accompanied by right hemispheric infarction or post-circulation infarction; (v) severe auditory disorders or no N1 potentials evoked in bilateral hemispheres; (vi) use of sedatives within 24 h before data collection; (vii) with complications such as severe electrolyte and metabolic disturbances and seizures; (viii) with ulceration or infection of the scalp; and (ix) pregnancy.

Clinical information, including age, sex, the interval between stroke onset and data collection, low-density volume on CT scan, lesion sites, GCS score and doses of mannitol at both

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collection sessions, were collected. All subjects' closest relatives or legal representatives gave their informed consent before data collection. This prospective observational study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University.

Stimulus paradigm

The paradigm used in our study is the passive oddball paradigm, with pure tones presented by e-prime3.0 software binaurally with insert earphones, with 2 types of stimuli: 1000 Hz frequent tones (90%, standard stimuli) and 1500 Hz rare tones (10%, deviant stimuli). Both types of stimuli have the same intensity (90 dB SPL) and time course (50 ms), with an interstimulus interval of 600 ms. Each data collection took no longer than 1 h, including a break.

ERP recording and analysis

EEG data were continuously recorded with NicoletOne software (Nicolet, American) using a 64-electrode EEG wireless 64A system. Electrodes were placed according to the international 10-10 system. Electrode impedances were all kept below 5KΩ. The continuous EEG data were recorded online at a sampling rate of 512 Hz with a bandpass filter of 0.05–70 Hz and referenced to CPz.

EEG data were offline band-passed filtered with a range of 0.5–40 Hz, and re-referenced to the averaged left and right mastoids (M1 and M2). Independent components analysis (ICA) was performed using the 'runica' algorithm from EEGLAB, and blinking artifacts were rejected. The continuous EEG data were segmented into 600-ms epochs (–100~500ms) and baseline correction was performed using the baseline prior to stimulus. Epochs contaminated with artifacts over ±100 uV were rejected before averaging.

The individual sweeps of every dataset were averaged for standard and deviant stimuli separately. For different ERP components, peak latencies were collected at Fz, as they were all considered to have a frontocentral topography, with specific latency windows for P1 (50–100 ms), N1 (101–150 ms), P2 (151–300 ms), and MMN (80–200 ms). Peak amplitudes were recognized as a peak maximum or minimum value in the particular latency windows.

Topographical changes of each component in both conditions were also compared between coma and awakening. ERP waveforms at each selected electrode were submitted to a time-frequency wavelet decomposition to identify the dominating frequencies across the time range and frequency changes from coma to awakening. Time-frequency analysis was also performed. The event-related spectral perturbations (ERSPs) were calculated with Morlet wavelet, and inter-trial coherences (ITCs) were also calculated to explore the phase synchronization across trials.

Statistical analysis

Differences in peak latencies were analyzed with a repeated-measures two-way analysis of variance (ANOVA) with Condition (standard, deviant) and Consciousness (coma, awakening) as the within-subject factors. Differences in peak amplitudes were analyzed with a repeated-measures three-way ANOVA with Site (13 levels: F3/F4/Fz/C3/C4/Cz/P3/P4/Pz/Fp1/Fp2/T7/T8), Condition (2 levels: standard, deviant), and Consciousness (2 levels: coma, awakening) as the within-subject factors. P values and degrees of freedom were judged based on the Geisser-Greenhouse correction when sphericity was violated. $P<0.05$ was considered to be statistically significant.

Results

Behavioral Responses

The age of the patients ranged from 65 to 79 (71.7±4.7) years, and the male-to-female ratio was 1: 1. The lesions were located in the left frontal, temporal, parietal, occipital, insular, and basal ganglia. The low-density volume on CT scans ranged from 309 to 866 (552.9±174.2) mm^3. All involved patients underwent 2 data collection sessions. The first session occurred at 4.1±2.6 days during the coma state with GCS score 6–7 (6.3±0.5), and the second session occurred at 13.8±0.8 days after stroke during the awakening state with GCS score 9–10 (9.3±0.3). The 3-month scores of the Glasgow Outcome Scale (GOS) were 2 in three patients and 3 in seven patients. All patients were treated with mannitol to alleviate the intracranial hypertension during the hospitalization, and the doses of mannitol were adjusted according to the extent of brain edema. Osmotic drugs, which relieve edema of brain cells through dehydration, indirectly affect the electrical activities of nerve cells, but not directly. Doses of other drugs, such as antiplatelet drugs, drugs to improve brain circulation, neuroprotective drugs, and antibiotics, were almost unchanged during the whole hospitalization and they also have little direct effect on electrical activities. Drugs that directly affect the electrical activities of brain cells, such as sedatives and antipsychotics, were not used in any eligible patients. Thus, the direct effects of drugs on patients' electrical responses can be largely ignored. The clinical characteristics are shown in detail in Table 1.

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Table 1. Demographic characteristics and clinical findings of the patients.

ID, sex*, age	Lesions' location**	Low-density volume (mm^3)	Intra-vascular therapy	Interval of onset-1st session (d)	Doses of mannitol-1st session	GCS at 1st session	Interval of onset-2nd session (d)	Doses of mannitol-2nd session	GCS at 2nd session	3m GOS
1, M, 78	FTPOI	553	No	9	125 ml q4h	E1V1M4	15	125 ml q6h	E4V1M4	3
2, M, 69	FTPOIB	866	No	5	125 ml q4h	E1V1M4	12	125 ml q6h	E4V1M4	2
3, F, 73	FPIB	440	No	2	125 ml q6h	E1V1M5	13	125 ml q8h	E4V1M5	3
4, F, 72	FTPIB	556	No	8	125 ml q4h	E1V1M4	14	125 ml q6h	E4V1M4	3
5, M, 69	FTOB	523	No	4	125 ml q4h	E1V1M4	14	125 ml q8h	E4V1M4	2
6, F, 65	FTPIB	479	No	3	125 ml q6h	E1V1M4	14	125 ml q8h	E4V1M5	3
7, M, 79	FTIB	309	No	1	125 ml q6h	E1V1M5	14	125 ml q8h	E4V1M5	3
8, F,73	FTIB	843	No	2	12 5ml q4h	E1V1M4	14	125 ml q6h	E4V1M4	2
9, M, 67	FTPIB	450	fail	3	125 ml q6h	E1V1M4	14	125 ml q8h	E4V1M4	3
10, F, 71	FTOB	510	No	4	125 ml q4h	E1V1M4	14	125 ml q8h	E4V1M4	3

* M – Male; F – Female; ** F – frontal; T – temporal; P – parietal; O – occipital; I – insular; B – basal ganglia.

Event-related potentials

The grand-average ERPs and difference waveforms during the coma and awakening states are shown in Figures 1 and 2, respectively.

P1

All patients had P1 waveforms at both sessions. Repeated-measures ANOVAs revealed no significant interactions of Condition×Consciousness [$F(1, 9)=2.44$, $p=0.15$] and no main effects of Condition [$F(1, 9)=0.24$, $p=0.64$] and Consciousness [$F(1, 9)=4.78$, $p=0.06$] for P1 latency. P1 was visibly larger, with a peak latency of approximately 50–100 ms after awakening, compared to that during the coma state. There were significant interactions of Site×Condition×Consciousness [$F(2.01, 18.13)=4.61$, $p=0.024$] to P1 amplitudes, but simple two-way interactions revealed no significant interaction of Condition×Consciousness at any selected sites ($p>0.05$) and Site×Consciousness [$F(1.24, 11.2)=2.25$, $p=0.16$], which indicated no significant differences in P1 amplitudes during coma and awakening.

N1

All patients had N1 waveforms at both sessions. Repeated-measures ANOVAs revealed no significant interactions of Condition×Consciousness [$F(1, 9)=1.71$, $p=0.22$] and no main effects of Condition [$F(1, 9)=0.12$, $p=0.73$] and Consciousness [$F(1, 9)=4.31$, $p=0.07$] for N1 latency. No significant interactions of Site×Condition×Consciousness [$F(2.08, 18.76)=1.34$, $p=0.29$] and no two-way interactions of any 2 factors [$F(1, 9)=0.40$, $p=0.54$; $F(2.94, 26.48)=2.25$, $p=0.11$; $F(2.08, 18.76)=2.17$, $p=0.14$] revealed any significance for the N1 amplitudes, which indicated no significant differences in N1 amplitudes between coma and awakening.

P2

All patients had P2 waveforms at both sessions. ANOVAs revealed significant interaction of Condition×Consciousness [$F(1, 9)=20.07$, $p=0.002$], and Consciousness showed a significant main effect for P2 latency in response to standard stimuli [$F(1, 9)=20.758$, $p=0.001$], but Consciousness did not for P2 latency in response to deviant stimuli [$F(1, 9)=1.082$, $p=0.325$]. The peak latency of P2 elicited by standard stimuli was significantly shorter after awakening (188.5±8.83 ms) than during the coma state (250.0±10.21 ms).

No significant Site×Condition×Consciousness interactions [$F(2.26, 20.36)=1.18$, $p=0.33$] and Condition×Consciousness interactions [$F(1, 9)=1.19$, $p=0.30$] emerged for P2 amplitudes, but two-way interactions revealed significant interaction of Site×Consciousness [$F(2.11, 19.03)=6.44$, $p=0.007$]. Analysis of single effects revealed that for standard stimuli, P2 amplitudes were significantly increased at Fz/Cz/Fp1/F3/C3/T7 and at Fp1 and F3 for deviant stimuli after awakening compared with those during the coma state ($p<0.05$) (see Table 2 for details).

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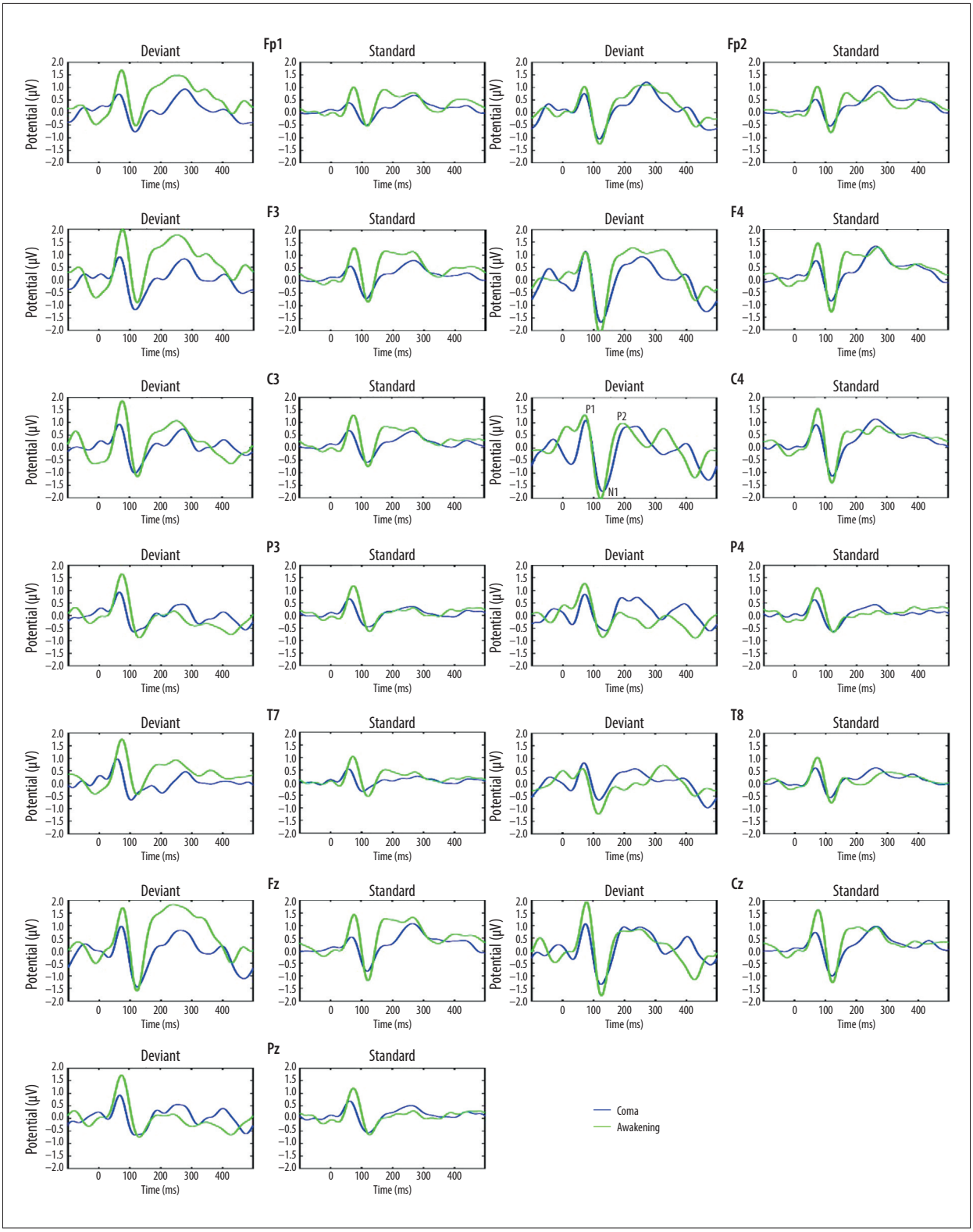

Figure 1. Grand-averaged ERP waveforms in response to both stimulus conditions during coma (blue lines) and awakening (green lines). For each electrode, the left panel indicated the ERPs evoked by deviant stimulation and the right panel indicated ERPs evoked by standard stimulation. For example, P1, N1 and P2 are recognized and marked at the electrode of C4.

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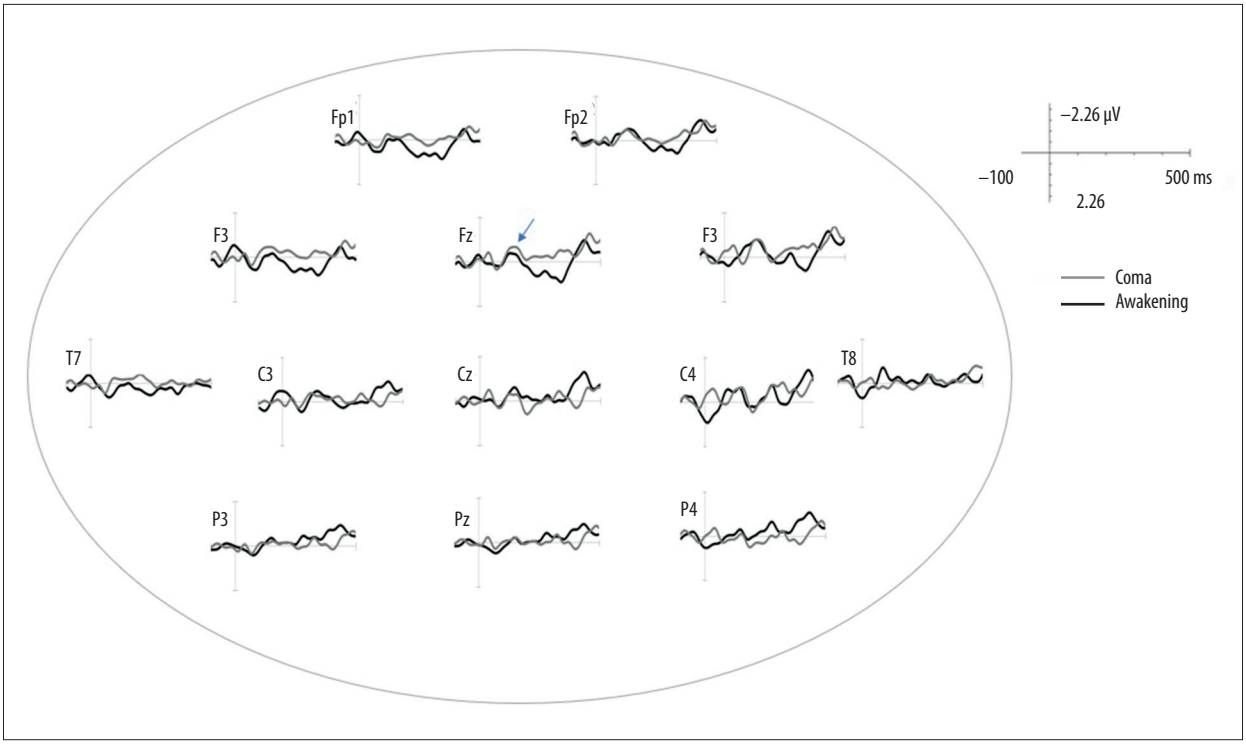

Figure 2. Difference waveforms for coma (grey lines) and awakening (black lines) states. MMN was recognized as the most negative deflection at 80–200 ms, as indicated by the arrow.

Table 2. P2 amplitudes in response to both stimuli at Fz, Cz, Fp1, F3, C3, and T7.

Condition	Consciousness state	Fz (μV)	Cz (μV)	Fp1 (μV)	F3 (μV)	C3 (μV)	T7 (μV)
Standard	Coma	0.77±0.86	0.73±0.45	0.61±0.49	0.78±0.34	0.84±0.17	0.46±0.12
	Awakening	1.70±0.55*	1.18±0.29*	1.14±0.09*	1.49±0.40*	1.01±0.04*	0.58±0.07*
Deviant	Coma	0.57±1.03	1.42±0.39	0.65±0.49	0.61±0.87	0.82±0.11	0.43±0.32
	Awakening	1.54±0.99	1.16±0.19	1.12±0.28*	1.35±0.47*	0.67±0.39	0.94±0.80

* p<0.05.

MMN

In coma state, MMN could be elicited over both hemispheres in 4 patients, but could not be elicited in 6 patients. During awakening, MMN were elicited over bilateral hemispheres in 6 patients, diminished over bilateral hemispheres in 2 patients, and only be elicited over the right hemisphere in 2 patients. 6 patients in whom MMN was diminished during the coma state all recovered to awakening; and in 4 of them, MMN reappeared. There was no significant difference in MMN latency between coma and awakening states (127.0±15.0 *vs.* 119.5±22.5 ms, p=0.14). The interaction between Consciousness*Site had no significant effect on MMN amplitude [F(1.39, 12.48)=3.56, P=0.073], but Consciousness and Site had main effect on MMN amplitude [F (1, 9)=14.26, p=0.004; F (2.23, 20.10)=3.20, p=0.057]. That is to say, the amplitudes of MMN were different in coma and awakening states, and the amplitudes of MMN were also different at different sites.

Topography

P1

As shown in Figure 3, during the coma stage, P1 amplitudes in response to both stimuli initiated in the whole brain areas synchronously at 50–75 ms, which later decreased and became limited to the local right centroparietal leads. Consistent with the distribution in coma, larger P1 amplitudes evoked by both stimuli were prominent at almost all sites at 50–75 ms after awakening, but at 75–100 ms, its topography shrank and was

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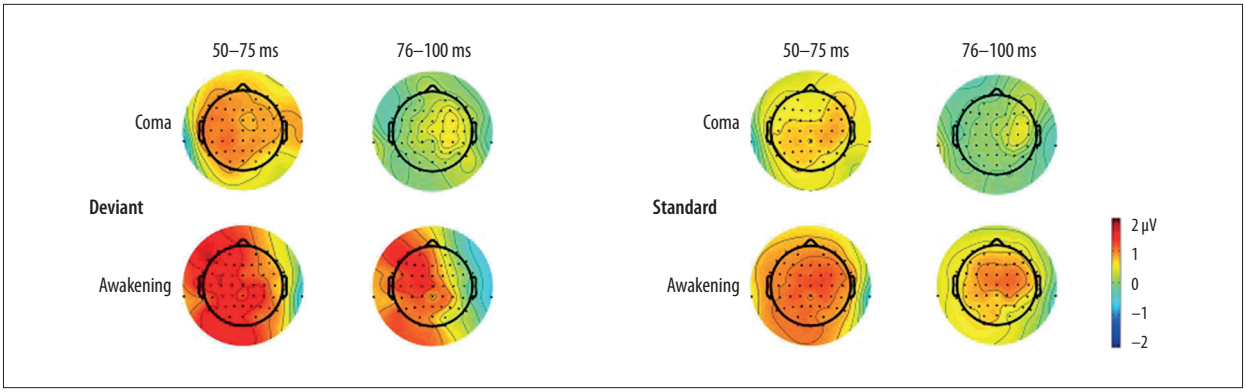

Figure 3. Topography of peak amplitudes for P1 in response to both stimuli during coma and awakening. As shown in the figure, during coma state, P1 amplitude appeared at 50–75 ms and attenuated at 76–100 ms. It increased to almost whole scalp during awakening, but the topography did not significantly change, especially at 50–75 ms, for both stimulus conditions.

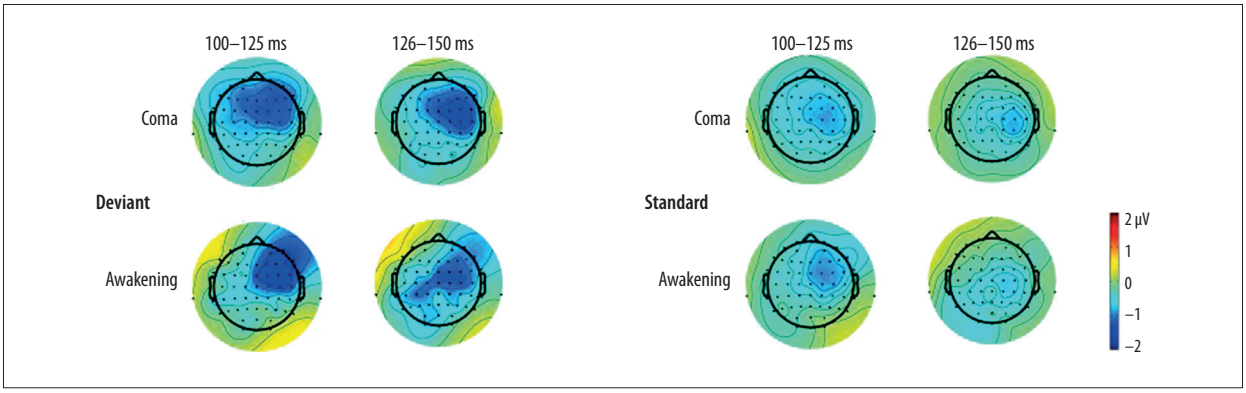

Figure 4. Topography of peak amplitudes for N1 in response to both stimuli during coma and awakening. As shown in the figure, the topography did not significantly change after awakening from that during the coma state, for both conditions.

localized to the left frontocentral areas for the deviant condition and central regions for the standard condition.

N1

N1 topographies were right frontal for both standard and deviant stimuli in the coma and awakening states, as shown in Figure 4. N1 latencies and durations in response to either condition were also similar between both consciousness states.

P2

As shown in Figure 5, the P2 scalp topographies in response to either standard or deviant stimuli were different between coma and awakening states. For P2 elicited by standard stimuli, during the coma state, it began to appear at 200–225 ms with a right frontal predominance, and the distribution pattern did not change over time. After awakening, P2 appeared earlier (at 151–175 ms after stimulus) and was distributed symmetrically in the frontal areas, with no changes over time. Interestingly, P2 in response to deviant stimuli in the coma state began to appear at 176–200 ms and was right frontocentral; it gradually shifted forward to the right frontal area and was finally attenuated at prefrontal areas. After awakening, P2 appeared earlier (at 151–175 ms) from the left frontal area and was prominent in the frontal area, with a slight bias to the left side. In summary, P2 in the awakening state appeared earlier and lasted much longer than those in the coma state, and the topography of P2 elicited by deviant stimuli markedly changed from coma to awakening.

MMN

The MMN topography of amplitude is shown in Figure 6, demonstrating that in the coma state, MMN appeared later (at about 100 ms after stimulus) than that during the awakening state (at about 75 ms after stimulus), but the distribution did not obviously change, localizing in the right frontocentral areas. This indicates that MMN scalp distribution was not affected by the arousal level, but the response speed was faster after awakening than that in the coma state.

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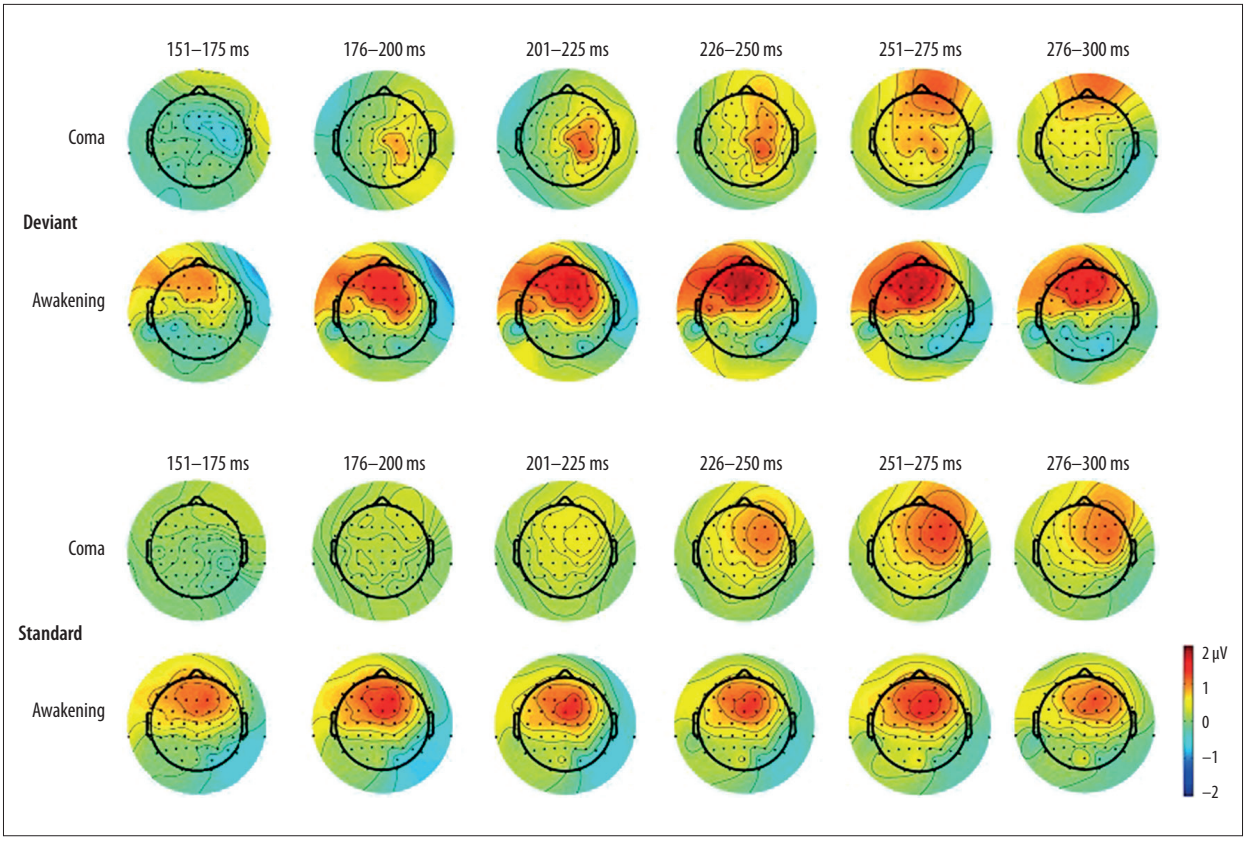

Figure 5. Topography of amplitudes for P2 in response to both stimuli during coma and awakening. As shown in the figure, the topographical distribution of P2 elicited by deviant stimuli significantly changed after awakening compared with that during coma state.

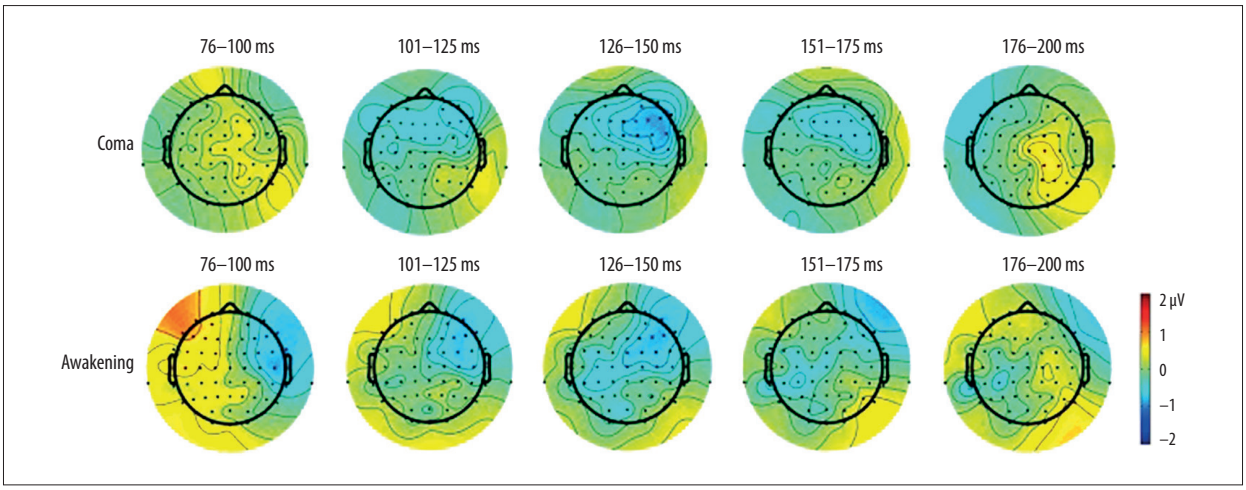

Figure 6. Topography of MMN amplitudes during coma and awakening states. It was mainly distributed in the right frontotemporal areas and no significant differences were seen between the topographical distribution of coma and awakening states.

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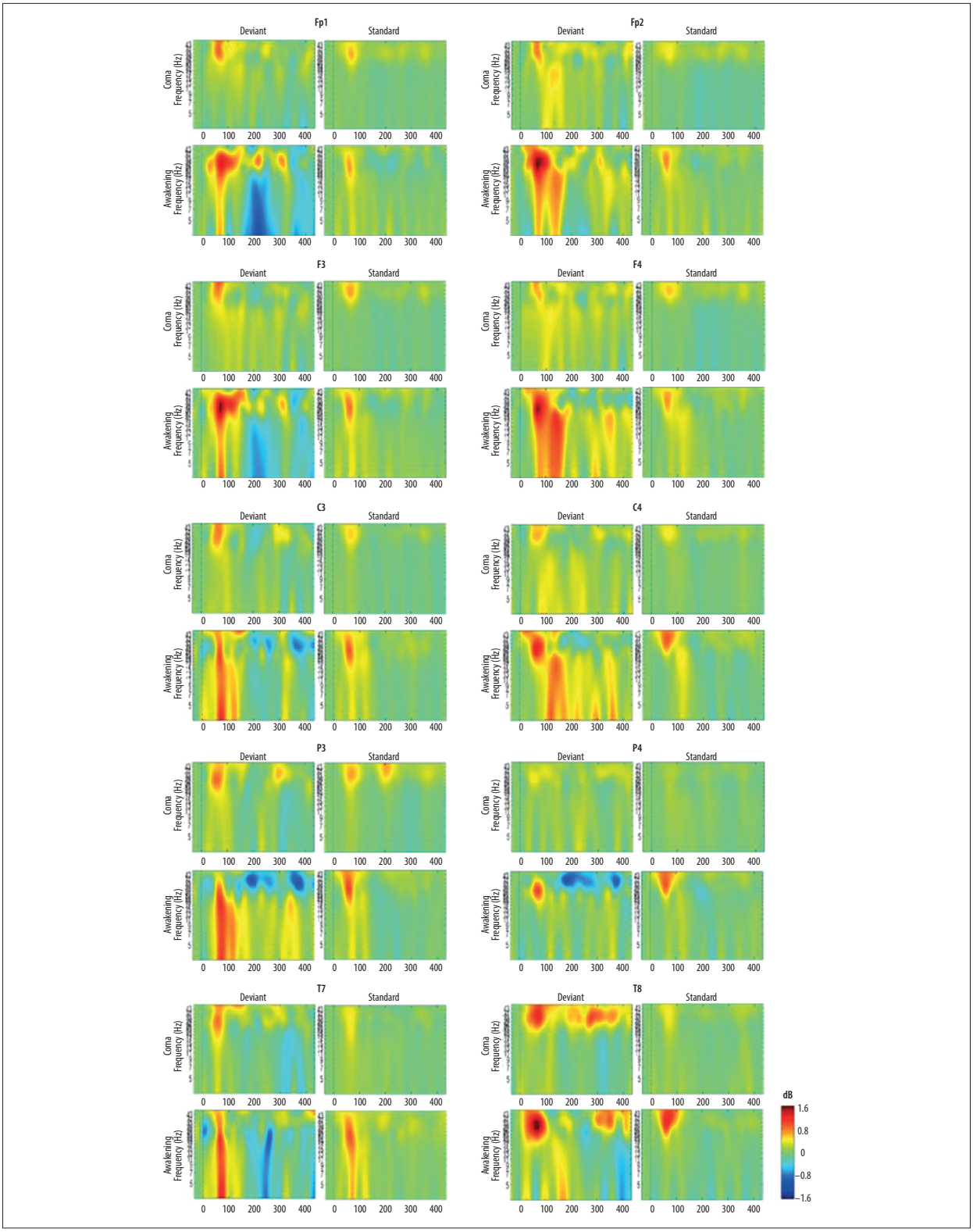

Figure 7. ERSPs at each electrode in response to both stimuli (left for deviant and right for standard stimulus) during coma and awakening states. During the coma state (**upper panel for each electrode**), there were no prominent activities of any frequency bands in the bilateral hemisphere. However, after awakening (**lower panel for each electrode**), obvious activities of broader frequency bands in response to both stimuli were seen at 50–150ms.

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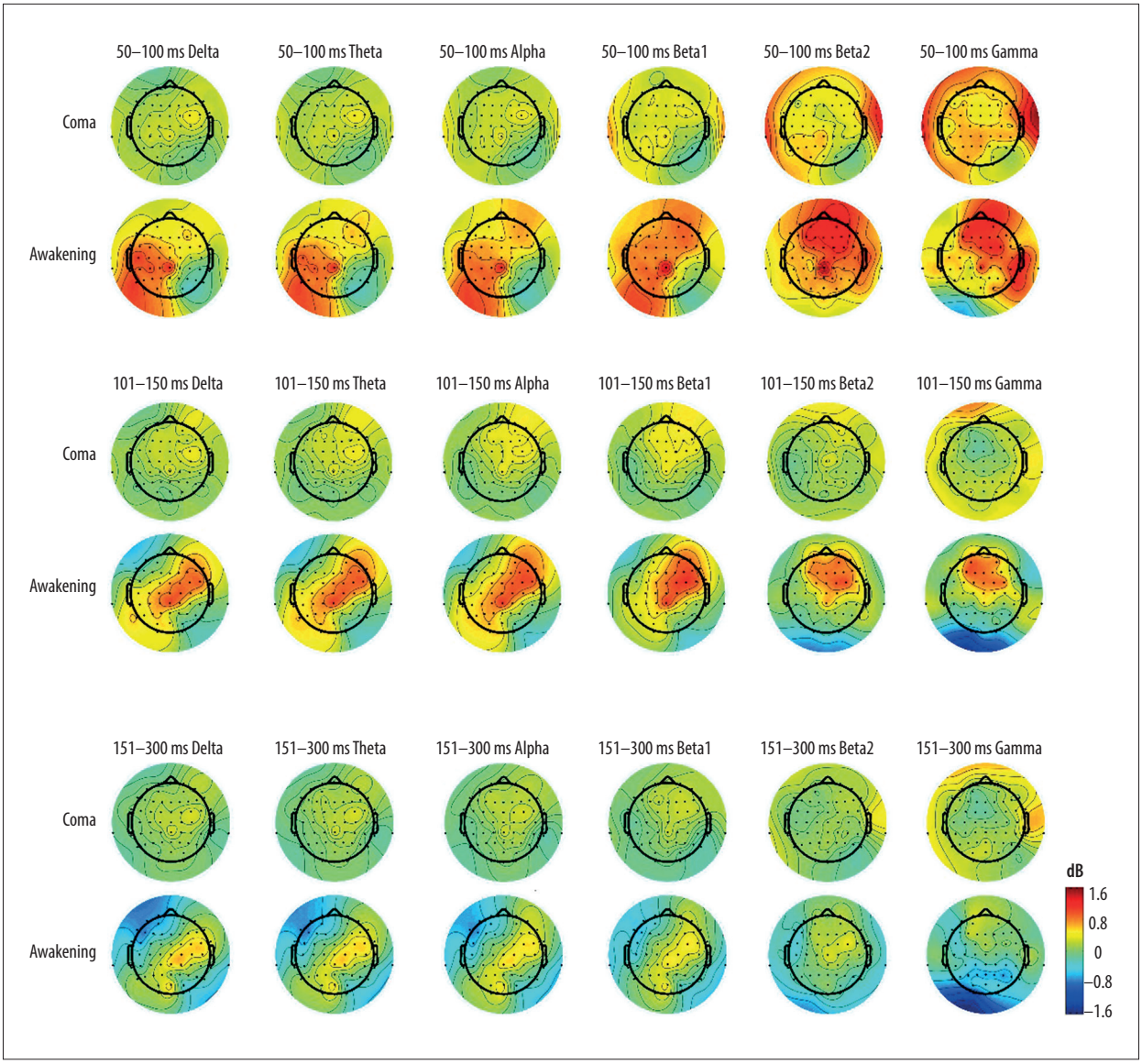

Figure 8. Topography of each frequency band in response to deviant stimulus during coma and awakening states. Distinct brain regions are recruited to work together with multiple frequency activities in dynamic processing of the sensory stimulus.

Time-frequency analysis

Event-related spectral perturbations (ERSPs)

ERSPs of the ERPs from 3 to 48 Hz at each selected electrode are shown in Figure 7, and the topographical distribution of each frequency range within the time windows of P1, N1, and P2 are shown in Figure 8.

During the coma state, only weak activities of β2 (20–30Hz) and γ (>30 Hz) in the time window of P1 (50–100 ms after stimulus) evoked by both stimuli were seen, with no obviously prominent scalp distribution. During the awakening state, responses to the standard stimulus were similar to that of the coma state, but deviant stimulus elicited enhanced frequency activities of broader ranges, including δ (<4 Hz), θ (4–7 Hz), α (8–13 Hz), β1 (14–20 Hz), β2 (20–30 Hz), and γ (>30 Hz). Delta and theta activities were mainly distributed in the left temporo-centro-parietal regions, and alpha and beta1 activities were mainly distributed in the left temporo-centro-parietal regions and both frontal lobes. The beta2 and gamma activities were located in both frontal and right temporal regions. During the time window of N1 (100–150 ms), no obvious activities were elicited in either hemisphere in the coma state. In the awakening state, responses to the standard stimulus were seen in the whole brain, but obvious delta, theta, alpha, and beta1

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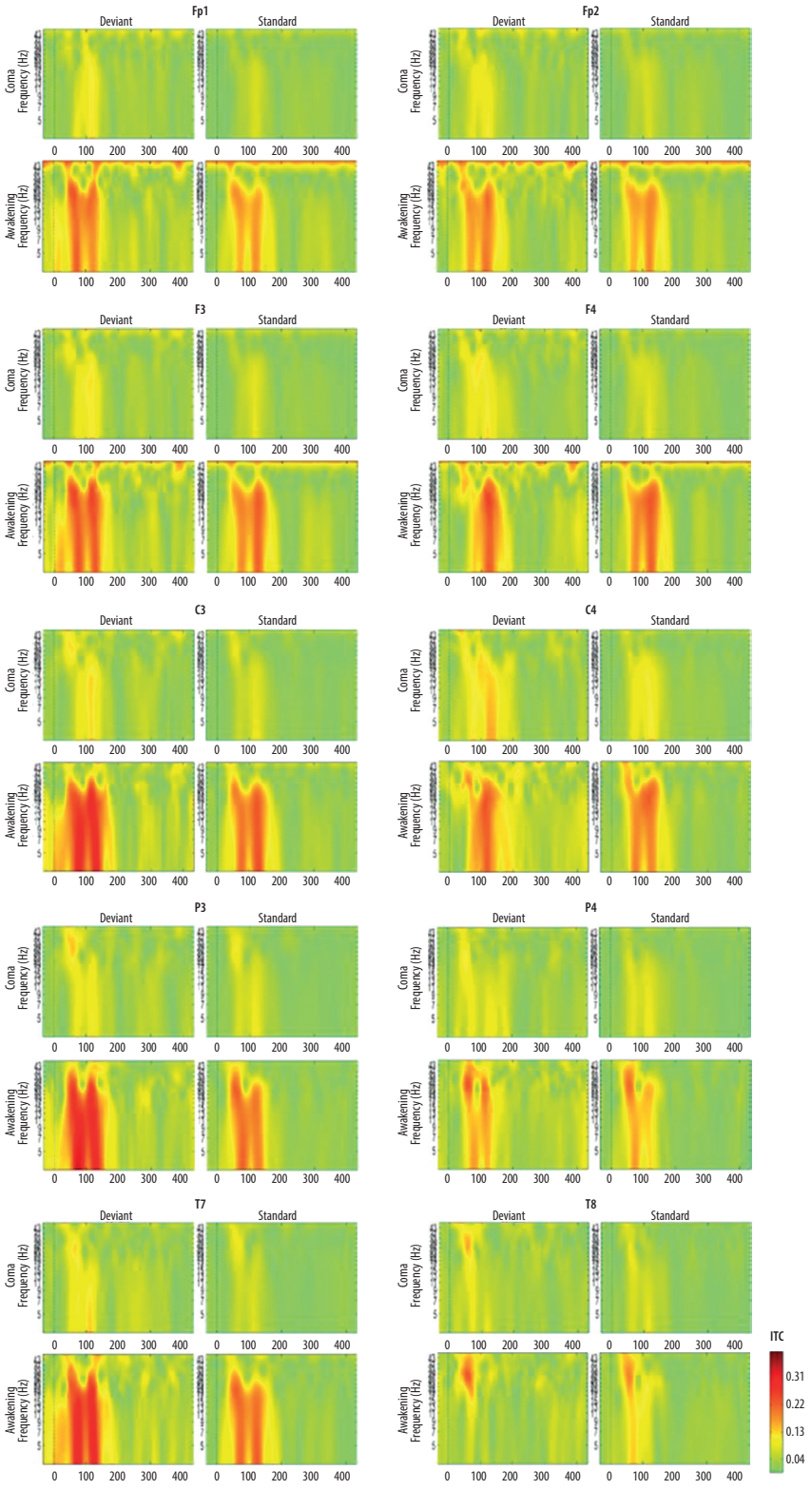

Figure 9. ITCs in response to both stimuli during coma (**upper panel for each electrode**) and awakening (**lower panel for each electrode**). For each condition, ITCs were more consistent from delta to gamma bands after awakening than those in the coma state.

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activities in the right fronto-centro-parietal regions and beta2 and gamma activities were seen in response to deviant stimulus. During the time window of P2 (150–300 ms), no obvious activities could be seen in the coma state and no activities were seen in response to the standard stimulus in the awakening state. However, delta, theta, alpha, and beta1 activities evoked by deviant stimulus in the right centroparietal regions and beta2 and gamma activities in both frontal lobes were evident, but these activities were all weaker than those during the time range of 50–150 ms.

In summary, responses to both stimuli in the bilateral hemispheres were significantly decreased in the coma state, with no differences between the 2 stimuli or among the brain regions. In contrast, in the awakening state, the responses of both hemispheres to deviant stimuli were significantly enhanced, with more frequency ranges and different topographical distributions.

Inter-trial coherences

Inter-trial coherences (ITCs) are shown in Figure 9. During coma state, the inter-trial phase coherences of both standard and deviant stimuli were poor, meaning that a fixed frequency activity at a fixed time point could be evoked by repeated stimulation. In contrast, during the awakening state, the inter-trial phase consistency in response to both stimuli in the time windows of 50–100 ms and 100–150 ms was obviously enhanced, suggesting that the responses to stimuli were time-locked and phase-locked.

Discussion

Our study has several major findings. First, the peak latencies and amplitudes of P1 and N1 evoked by both stimuli did not significantly change after awakening. However, the latency of P2 to standard stimuli was much shorter, and the amplitudes in response to both stimuli significantly increased. Second, a surprising topographical modification in P2 amplitudes in response to deviant tones was observed, shifting from the right centro-parietal-frontal areas during the coma state to the left frontal-midline areas after awakening. Finally, no obvious activities of any frequency band with poor inter-trial phase synchronization were elicited in bilateral hemisphere during the coma state, whereas after awakening, broad frequency bands (δ to γ) with higher inter-trial phase coherence in response to both stimuli were observed in the time windows of P1, N1, and P2.

P1 and awakening

Only a few studies have focused on the correlation between P1 and consciousness. A study in 1986 investigated P1 changes during sleep and found that the amplitude of P1 significantly decreased or disappeared during the non-rapid eye movement sleep (NREM) stage and reappeared at the rapid eye movement sleep (REM) stage. In addition, the amplitude was positively correlated with the degree of awakening [12]. An anesthesia study found that the P1 amplitude did not change significantly during the sedation stage with propofol at the initial stage of anesthesia, but decreased significantly during the unconscious stage [13]. Another study on coma after brain injury showed that the bilateral existence of P1 predicted the recovery of patients, while the absence suggested a persistent vegetative state [14]. In our study, significant P1 elicited by both standard and deviant stimuli was observed during coma and awakening, and all patients recovered at approximately 14 days, when the amplitude of P1 tended to increase.

However, the neurophysiological mechanism underlying the generation of P1 remains unclear. The intralaminar thalamus and brainstem reticular formation play significant roles in the generation of wave "A" in cats [15], the homologous component of P1 in humans [16]. P1 is speculated to originate from a part of the brainstem reticular ascending activation system, which projects upward to the thalamus and throughout the cerebral cortex. Thus, P1 may be related to arousal regulation, but only an increasing trend of P1 amplitudes appeared after awakening in this study. Although the topographical distribution was not obviously changed for P1 in our study, our results are not contradictory to previous studies.

N1 and awakening

The relationship between N1 and consciousness is still under debate. Previous studies reported that the N1 amplitude decreased gradually during sleep onset, significantly decreased during the NREM stage [17], or even disappeared [18], and appeared again during the REM stage, reaching 25–50% of the amplitude observed in awakening [19]. N1 can still exist in deep sedation induced by propofol anesthesia [17]. However, N1 disappears when transitioning to the unconscious state, which indicates that the disappearance of N1 is the sign of transitioning from consciousness to unconsciousness [20]. Our study showed that significant N1 waves can be elicited in both coma and awakening states with no significant difference in amplitude and topographical distribution, which reveals there is no obvious relationship between N1 and awakening.

Most scholars believe that N1 originates from the auditory cortex of the superior temporal gyrus [21], which is related to the information extraction process at the initial stage of the sensory process or the secondary distribution of information processing beyond the primary auditory cortex. The hippocampus, dorsolateral prefrontal cortex, and thalamus may also participate in this process [22].

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P2 and awakening

As one of the least researched ERP components, the functional significance of P2 is quite unclear. The amplitude of P2 increases during sleep onset and continues to rise until the NREM period [23]. In phase I and phase II of NREM sleep, the amplitude of P2 in response to a deviant stimulus was reported to increase [19] or remain unchanged [24,25]. In another study, P2 existed in phase II of NREM sleep and REM sleep. In contrast, the P2 amplitude was reported to decrease or disappear during the anesthesia stage [26]. In our study, both standard and deviant stimuli elicited obvious P2, not only in the coma state but also in the awakening state. The amplitude of P2 was higher in the awakening state, especially in the left frontal-temporal and midline areas. Our results seem to be contradictory to previous studies. However, the increase in P2 amplitude in sleep was compared to that during normal wakefulness, and the increase in P2 after awakening in our study was compared to that during the coma state.

Generally, the maximum amplitude of P2 appears at the vertex (Cz), while the scalp distribution of P2 related to coma and awakening has not been reported. In our study, the maximum amplitude of P2 in coma was highest in the right parietal region, and after awakening, it shifted to the left frontal-midline area. Another study also found that the scalp distribution of P2 during sleep is different from that during wakefulness [27]. The shift of the scalp distribution of P2 may indicate that the underlying process of P2 generation is changed from coma to awakening.

According to previous studies, P2 is involved in the conjunction of exogenous and endogenous processes. P2 was sensitive to the extent of auditory frequency difference between standard and deviant tones [28], indicating that P2 reflects the rapid access and delicate process of specific physical features of the stimulus [29]. Facilitated access may have led to improvements in perceptual comparison and discrimination. In addition to the role of processing physical features of stimuli, P2 seems to have endogenous properties in pre-awareness. In paradigms for discrimination, P2 was thought to play an essential role in the classification of different stimuli [27]. In paradigms for selective attention, P2 was believed to be involved in blocking out the irrelevant stimuli [30]. Other speculations regarded P2 as a pre-attentive alerting mechanism contributing to the perception improvement [31] or an index of inhibitory processes modulating the thresholds for conscious perception [32,33]. The combined process of exogenous and endogenous features leads to the involvement of P2 in the integrity of cortico-thalamic pathways [34].

Although no similar studies have focused on the association of P2 with consciousness, the argument in other studies that P2 originates in the secondary auditory cortex and reflects the synchronicity of neural activities in the thalamocortical pathways [35,36] supports our results to a certain extent, indicating that P2 plays an essential role in the maintenance of arousal. The above studies also regarded P2 as a pre-awareness process for stimuli. In other words, P2 may reflect the exogenous process of specific features as well as the endogenous pre-awareness process for stimuli. Both processes are involved in the early stage of coma recovery. In this study, the amplitude of P2 increased and the topographical distribution changed, which may indicate that the process of P2 generation differs between coma and awakening.

The neurophysiological mechanisms underlying the generation of P2 remain quite confusing. The neural basis of the P2 component is not well known, and multiple sources may be involved in its generation, including the auditory output of the mesencephalic reticular activating system [37,38], planum temporale [39], and Brodmann's area 22 [39]. The underlying mechanisms of P2 enhancement and overlapping activities remain less defined [40]. In short, a clear identification of its cortical generators is still missing, and the understanding of the functional significance of the auditory P2 component remains very superficial [41].

MMN and awakening

MMN is a well-established predictor of awakening in non-sedated comatose patients [42], and its prognostic value in deeply sedated critically ill patients also has recently been investigated. MMN can be observed in deeply sedated critically ill patients and can help predict subsequent awakening [43]. There has been only 1 study examining the effects of alterations in brain arousal on EPs, but it focused on the ERP alterations before sleep onset [44]. In the present study, no effect was found of EEG-vigilance stages on MMN. In this study, no MMNs were elicited over bilateral hemispheres in 6 out of 10 patients, but all of them woke up at session 2, which does not fully support the view that MMN is a good predictor of coma recovery. Therefore, being able to recover from coma may be more determined by coma etiology and lesion site. The predictive value of MMN may be different for coma with different etiologies. Previous studies have not compared the predictive value of MMN for coma with different causes, which should be stratified in further studies.

Time-frequency information

We found no statistically significant increases in the amplitudes of P1 and N1, but significant frequency activities were observed after awakening, suggesting that time-frequency information is more sensitive than the amplitudes in identifying consciousness and, perhaps, other functions. In the present

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study, evoked oscillations in the bilateral hemisphere were profoundly inhibited during the coma state, with poor phase synchronization between the trials. After awakening, obvious activities with broader frequency ranges and consistent inter-trial phase synchronization were observed in the bilateral hemisphere. Different frequency activities were distributed in different brain regions, suggesting that distinct brain structures are recruited to work together in dynamic processing of sensory stimuli.

A number of studies have focused on the event-related oscillations in numbers of cognitive paradigms. Delta, theta, alpha, beta, and gamma oscillations all participate in different tasks and cognitive processes. The delta oscillation is thought to be related to attention, perception, signal detection, decision making, and other cognitive processes [45]. Event-related theta oscillation is thought to play an important role in the processes of memory, attention, and cognition [46]. There is still no clear explanation for the general function of alpha oscillatory activity, which may be a building block of multiple physiological sensory, motor, and memory functions [47]. Evoked beta oscillatory activity is thought to be associated with projection into the sensory-specific cortex [48]. Gamma oscillation is induced by various stimuli or tasks, and is related to several cognitive functions [49]. However, few studies have shown that evoked oscillations or event-related oscillations are related to consciousness. Evoked event-related oscillations may provide more information about cognitive functions in unconscious or unresponsive patients.

We also performed EEG for these recruited patients and found that the patterns of functional connectivity had significantly changed after awakening compared with that during coma (unpublished data). All these findings provide more information related to consciousness and may also serve as potential predictors of outcome in LHI patients in the future. There is also compelling evidence that stroke outcome is strongly influenced and can be predicted by a variety of factors related to metabolic homeostasis [50], immune biomarkers [51], perfusion disturbances [52], inflammatory response [53,54], and drug actions [55]. EEG may also contribute to prediction of outcome following coma [56]. All these factors may act either at the brain site of damage or systemic level and influence neurovascular recovery. Multidimensional evaluation of stroke patients is of great importance in predicting their outcome. In addition, taking into account the heterogeneity of these factors, their reciprocal interaction, and the continuing expansion of electronic medical records, artificial intelligence algorithms might contribute to predicting stroke recovery by a personalized approach.

Conclusions

This study provides data on the underlying neurophysiological changes in the coma recovery process in left LHI patients. P2 may be a central index of awakening and a component of the arousal system. To the best of our knowledge, this study is the first to explore the relationship between exogenous ERP components and waking up from coma. Furthermore, changes in scalp topographical patterns may suggest different P2 generation processes in coma and awakening, and provide evidence for target selection in wake-promotion therapy. However, the correlation between MMN and consciousness in patients with large left hemispheric infarction is still unclear. Changes of time-frequency information may provide more information during coma recovery, perhaps including underlying cognitive processing of the sensory stimulus.

Limitations

Our study has several limitations. Firstly, the sample size was relatively small. Secondly, we only included the left LHI patients, as the ERPs may be differently affected in patients with left and right LHI, and we plan to enroll right LHI patients in another study. Thirdly, the results need to be validated in other comatose patients.

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Conflict of interest

None.

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