# Mismatch negativity to the patient's own name in chronic disorders of consciousness

Pengmin Qin[a], Haibo Di[b], Xiaodan Yan[a], Senming Yu[c], Dan Yu[c], Steven Laureys[d], Xuchu Weng[a,*]

[a] Laboratory for Higher Brain Functions, Institute of Psychology, Chinese Academy of Sciences, 4A Datun Road, Chaoyang District, Beijing 100101, China
[b] Hangzhou Normal University, Hangzhou, China
[c] Rehabilitation Center for Brain Damage, Wujing Hospital of Hangzhou City, Hangzhou, China
[d] Coma Science Group, Cyclotron Research Centre and Neurology Department, University of Liège, Liège, Belgium

## ARTICLE INFO

## ABSTRACT

Previous studies implicated potential value of mismatch negativity (MMN) in predicting recovery of consciousness in patients with disorders of consciousness (DOC). We have adopted a novel MMN evoked by subject's own name (SON), a self-referential stimulus thought to be powerful in evoking residual brain activity, and examined the correlation between the MMN and recovery of consciousness in patients with chronic (>1 month) DOC. Twelve patients and 12 age-matched healthy controls were investigated. The patients were diagnosed as coma ($n = 4$), vegetative state (VS, $n = 6$), and minimally conscious state (MCS, $n = 2$), mainly based on the JFK Coma Recovery Scale-Revised. The SON-evoked MMN (SON-MMN) was present in seven patients. Critically, the presence of SON-MMN was significantly correlated with recovery of consciousness. While four of the five patients (three VS and two coma) showing SON-MMN changed to MCS 3 months later, the rest of the patients (three VS and two coma) without SON-MMN failed to show any clinical improvement. Our study thus illustrates that the subject's own name is effective in evoking MMN in patients with DOC, and that SON-MMN has potential prognostic values in predicting recovery of consciousness.

© 2008 Elsevier Ireland Ltd. All rights reserved.

Self-referential stimuli such as the subject's own name (SON) are thought to be more effective to induce brain activities in patients with disorders of consciousness (DOC) compared to other stimulation types [14]. The SON could evoke cognitive event-related potential (ERP) waveforms [11,16,18,21] and induce activation in widespread brain areas [4,15,22] in patients with DOC who remain in coma, vegetative state (VS), and minimally conscious state (MCS). In our recent fMRI study, we have showed that the SON-induced brain activation seems to be highly correlated with the recovery of consciousness in VS patients [4]. However, the availability and feasibility of fMRI is relatively poor as compared to ERP technique, another promising objective measure of residual brain function [3]. Moreover, this technique can be used at the bedside, which is particularly significant for clinical use on patients with severe brain injury. Among the ERP components, mismatch negativity (MMN) has been given special attention in the field. For example, MMN evoked by non-self-related stimuli is shown to be able to predict awakening in acute coma [5]. This MMN also seems to have

potential value in predicting clinical improvement in patients with chronic DOC [13,25]. Nonetheless, the prognostic value of MMN evoked by self-referential stimuli has not yet been properly evaluated. Based on our previous study [4] and those of others [8], we predict that the presence of SON-evoked MMN (SON-MMN) will indicate potentially better clinical outcome in patients with chronic DOC.

MMN is regarded as an indicator of pre-attentive sensory memory processes. The conventional MMN is obtained by subtracting ERPs to standard stimuli from ERPs to deviant stimuli (standard and deviant stimuli in the same Oddball procedure) [17]. Since this type of MMN is prone to both physical properties and neural refractoriness, in the present study we have employed a protocol designed to minimize the effects of these factors similar to Jacobsen and Schroger [10]. In the protocol, the brain response to a deviant stimulus in the Oddball block (consisting standard and deviant stimuli) is compared with the brain response to the same stimulus in the Control blocks (i.e., the stimulus has the same probability as the deviant in the Oddball block).

We studied 12 patients with chronic (>1 month) DOC (Table 1) and 12 age-matched healthy controls (mean ± S.D., 42 ± 10 years; range 28–58). The patients were first assessed by conventional neurological examinations and the Glasgow-Liège Scale (GLS) [2] (i.e.,

* Corresponding author. Tel.: +86 10 64854476; fax: +86 10 64872070.
E-mail address: wengxc@psych.ac.cn (X. Weng).

**Table 1**
Patients' demographic and clinical data.

| Patient number/gender/age (years) | Clinical diagnosis | Cause | Time of ERP recording (months after insult) | MRI findings | Deep tendon reflexes | Babinski sign | GLS score (EVMR) |
|---|---|---|---|---|---|---|---|
| 1/M/13 | VS | Trauma | 2 M | Bilateral occipital and cerebellar lesions, ex-vacuo hydrocephalus | Increased | Bilateral | 4-2-4-5 |
| 2/M/52 | VS | Trauma | 4 M | Right frontal, temporal and parietal lesions, ex-vacuo hydrocephalus | Increased | Bilateral | 4-2-4-5 |
| 3/F/52 | VS | Trauma | 1 M | Right parietal and temporal hemorrhage | Absent | Bilateral | 4-T-3-4 |
| 4/M/48 | VS | Trauma | 2 M | Bilateral frontal and temporal subdural collections | Absent | Right | 4-T-4-5 |
| 5/M/60 | VS | Trauma | 2 M | Bilateral frontal and temporal contusions, ex-vacue hydrocephalus | Absent | Bilateral | 4-1-4-5 |
| 6/M/31 | VS | Anoxic | 2 M | atrophy with ex-vacuo hydrocephalus | Absent | Absent | 4-T-3-4 |
| 7/F/53 | coma | Trauma | 2 M | Right temporoparietal edema and hemorrhage | Absent | Bilateral | 1-1-2-5 |
| 8/F/41 | coma | Trauma | 1.5 M | ex-vacuo hydrocephalus | Increased | Bilateral | 1-T-4-5 |
| 9/M/34 | coma | Trauma | 2 M | Bilateral temporal and right frontal cortex lesions | Normal | Bilateral | 1-T-4-5 |
| 10/M/54 | coma | Trauma | 2 M | Right frontal, temporal and thalamic lesions | Increased | Bilateral | 1-1-3-5 |
| 11/M/58 | MCS | Trauma | 1 M | Right frontal and left temporal, occipital, parietal cortex lesions | Normal | Bilateral | 4-1-4-5 |
| 12/M/38 | MCS | Trauma | 6 M | Bilateral temporal and frontal cortex lesions | Normal | Bilateral | 4-1-3-5 |

GLS (Glasgow-Liège Scale); E (eye response); V (verbal); M (motor) are scored as in the Glasgow Coma Scale (GCS); R (brainstem reflexes: score of 5 indicates preserved fronto-orbicular, 4 indicates vertical oculovestibular). T: tracheal cannula.

the Glasgow Coma Scale [24] and standardized evaluation of brainstem reflexes). Clinical diagnoses of VS and MCS were based on the JFK Coma Recovery Scale-Revised (CRS-R), which comprises six subscales addressing auditory, visual, motor, oromotor, communication, and arousal functions, respectively [6]. Accordingly, the patients were diagnosed as coma ($n = 4$), VS ($n = 6$), and MCS ($n = 2$), at the time of ERP recording. Informed written consents were obtained from the healthy participants and the families of the patients, and the study was approved by the local Ethics Committees of the Institute of Psychology at Chinese Academy of Sciences and Zhejiang University School of Medicine.

There were two block conditions in the ERP recording: the Oddball block and the Control block. In the Oddball block, SONs, called by the same female voice, served as deviant stimuli (12.5% of all stimuli), and tones of 800 Hz as standard stimuli. The mean duration of SONs was $637 \pm 71$ ms, while tones of 800 Hz had a duration of 30 ms. The tones were presented binaurally at an 85 dB and the SONs at an 80 dB sound pressure level maximal intensity. The Control block included SONs and seven control stimuli (three names of other persons and four sine tones in different frequencies, 12.5% for each type of stimuli). There were 720 events in each block. Stimulus onset asynchrony (SOA) was randomized between 1100 and 1300 ms. In the Oddball block, deviants occurred in a pseudorandomized fashion with a constraint that two SONs could not be called in immediate successions, and stimuli in the Control block were presented without repetitions [10]. The order of the two blocks was counter-balanced across the subjects.

Healthy controls sat in a comfortable chair and were instructed to watch a self-selected silent movie on a computer during the experiment. For patients, data was acquired at the bedside. ERPs were recorded at Fz, Cz, and Pz (according to the International Ten-Twenty System) (a reference was put on the nose) using a Neuroscan NuAmps Amplifier with Ag/AgCl electrodes. Data was sampled at 1000 Hz with an analog bandpass of 0.1–100 Hz. Impedance of each electrode was kept below 5 kΩ and 50 Hz was notched. The electro-oculogram was recorded from two pairs of electrodes, one above and below the right eye and the other on the outer canthi of the two eyes. A ground electrode was placed on the middle of the forehead.

EOG artifacts were corrected using the method proposed by Semlitsch et al. [20]. All continuous EEG data was digitally filtered with a low pass filter at 30 Hz for N100. All continuous EEG data was digitally filtered with a bandpass of 3–30 Hz for MMN [5]. The EEG data were segmented in epochs of 600 ms, time-locked to stimuli onset, and included a pre-stimulus period of 100 ms. All epochs including voltage changes exceeding $\pm 50\,\mu V$ were automatically rejected and were averaged according to same stimuli type.

We identified two ERP components: N100 evoked by each stimulus type and the mismatch negativity evoked by subject's own name (denoted as SON-MMN), which was computed by subtracting averaged ERPs to SON in the Control block from averaged ERPs to SON in the Oddball block. The time window appropriate for N100 was defined on the basis of inspection of the average waveform (with peak within 100–200 ms after stimulus onset), and the mean amplitude in this window was measured in each single trial, separately at Fz and Cz [13]. One sample $t$-test then was used. If the mean amplitude was significantly different from zero ($p < 0.05$, with Bonferroni correction), N100 was judged as being present. For the SON-MMN, the mean amplitude in each trial of SON in both blocks was measured in an appropriate time window, which was defined on the basis of inspection of the difference waveform (with peak within 100–400 ms after stimulus onset), respectively, at Fz and Cz. The amplitude difference of the Oddball block and Control block at Fz or Cz was tested with an independent sample $t$-test. If the mean amplitude of the Oddball block was significantly different
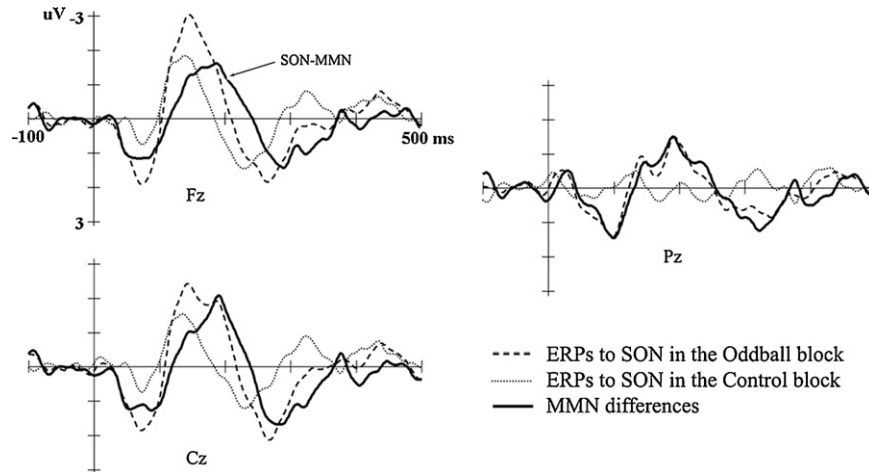
**Fig. 1.** Grand average event-related potentials at three midline electrodes. ERPs to SON in the Oddball block and in the Control block, and MMN differences in the control group ($n = 12$).

from the Control block and the polarity of the between-block difference corresponded to the conventional MMN, then the SON-MMN was judged as being present. The significance level was set at 0.05 (without Bonferroni correction). As the latency of MMN in patients was more delayed than in controls [5], an extended time window was adopted.

In order to assess the power for predicting recovery of consciousness of the two ERP components, the patients' conscious state was assessed again by CRS-R 3 months after ERP recording (6 months after acute brain injury), and correlation between the transition of conscious state and the presence of the ERP components was determined using Fisher's tests. Specifically, one variable was whether the patients emerged from VS (or coma) to MCS 3 months after ERP recording, and the other was whether the presence or absence of the ERP components. The data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

We found that N100 and SON-MMN were present in each of the 12 healthy controls (Fig. 1). The latency and amplitude of SON-MMN was $186 \pm 30$ ms (mean $\pm$ S.D.) and $-3.06 \pm 0.88 \, \mu$V (mean $\pm$ S.D.) (Cz), respectively.

In contrast, SON-MMN was present only in seven (two coma, three VS and two MCS) out of the 12 patients (Fig. 2). The amplitude and latency of SON-MMN in the patients were $216 \pm 67$ ms (mean $\pm$ S.D.) and $-2.80 \pm 1.23 \, \mu$V (mean $\pm$ S.D.) (Cz), and they were not significantly different from those in healthy controls. N100 was present in nine patients (three coma, four VS and two MCS) (Table 2). All of the seven patients with SON-MMN also showed N100, so did other two patients (patient 4 and patient 10) without SON-MMN.

Three months after the ERP recording, we re-assessed patients' conscious state. The data showed that six out of the seven patients with the presence of SON-MMN were diagnosed as MCS (four changed from coma or VS). None of the remaining five patients without SON-MMN (three VS, two coma) showed any clinical improvement in the 3 month follow-up (Table 2). The presence of SON-MMN was significantly correlated with the transition from coma/VS to MCS ($p < 0.05$), while no correlation was found between N100 and such transition ($p = 0.20$).

In this study, we obtained a reasonably high presence ratio of both SON-MMN and N100 in the patients with DOC (SON-
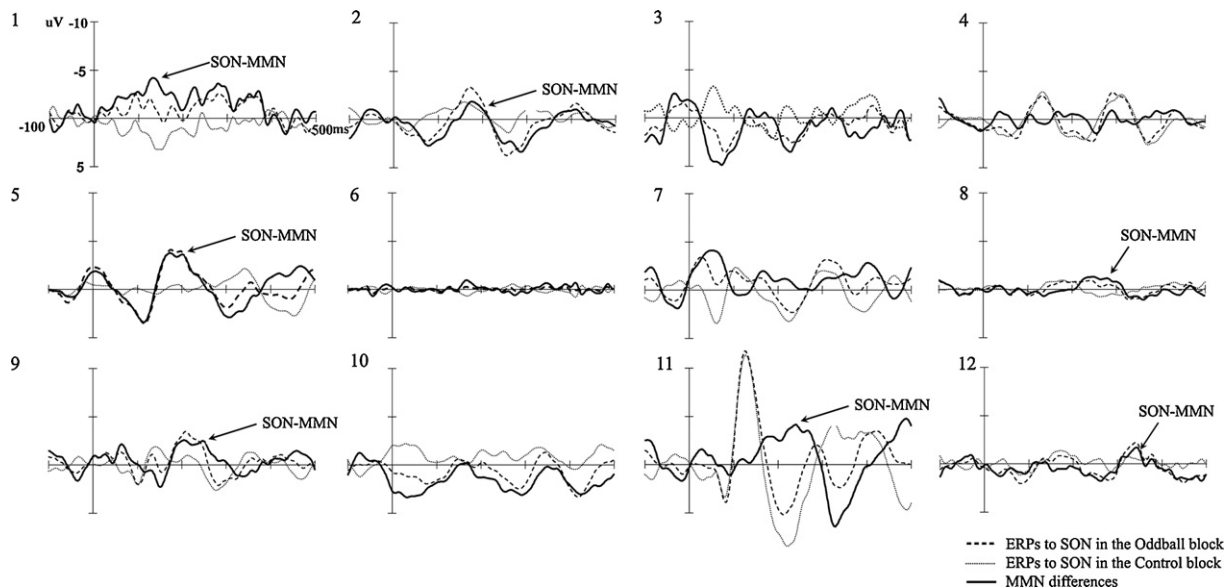


**Fig. 2.** Individual event-related potentials: ERPs to SON in the Oddball block, ERPs to SON in the Control block and MMN differences are shown at Cz. SON-MMN is indicated if significant ($p < 0.05$).

**Table 2**
Patient diagnosis and JFK CRS-R scores at the time of ERP recording and 3 months later, presence of ERPs.

| Patients | Time of ERP recording | | N100 | SON-MMN | Three month after ERP recording | |
|---|---|---|---|---|---|---|
| | Clinical diagnosis | JFK CRS-R score | | | Clinical diagnosis | JFK CRS-R score |
| 11 | MCS | 1-1-3-1-0-2 | + | + | MCS | 1-1-3-1-0-2 |
| 12 | MCS | 0-1-1-0-1-2 | + | + | MCS | 0-2-2-2-1-2 |
| 1 | VS | 1-1-2-2-0-2 | + | + | MCS | 1-1-3-2-0-2 |
| 2 | VS | 1-1-2-1-0-2 | + | + | MCS | 2-3-2-1-0-2 |
| 5 | VS | 1-0-2-0-0-2 | + | + | MCS | 1-1-3-1-0-2 |
| 9 | coma | 1-0-2-0-0-0 | + | + | MCS | 1-3-2-1-0-2 |
| 8 | coma | 1-0-2-0-0-0 | + | + | VS | 1-1-1-1-0-2 |
| 10 | coma | 0-0-1-0-0-0 | + | − | VS | 0-0-1-0-0-0 |
| 4 | VS | 1-1-2-1-0-2 | + | − | VS | 1-1-2-1-0-2 |
| 7 | coma | 0-0-1-1-0-0 | − | − | VS | 2-1-1-1-0-2 |
| 3 | VS | 0-0-1-1-0-2 | − | − | VS | 0-0-1-1-0-2 |
| 6 | VS | 0-0-1-0-0-2 | − | − | VS | 0-0-1-0-0-2 |

JFK Coma Recovery Scale-Revised (CRS-R) subscales: auditory function; visual function; motor function; oromotor/verbal function; communication; arousal. "+", significant at 0.05 level, "−", not significant at 0.05 level.

MMN in 7/12, N100 in 9/12). Only SON-MMN showed a significant prognostic value. Four out of five unconscious patients showing a SON-MMN response subsequently recovered to be in MCS 3 months after ERP recording, while none of the five patients without SON-MMN regained consciousness. The SON-MMN thus was significantly correlated with transition from VS to MCS. In contrast, N100 was a poor indicator of the recovery of consciousness. Four out of the seven unconscious patients with N100 changed to MCS, while the other three did not show any clinical improvement. One recent review also suggested that N100 tended to be an inferior predictor than MMN [3]. Our current ERP results were in line with our previous fMRI study showing that brain activation evoked by SON could predict the outcome of patients with DOC [4]. In our previous study, subsequent recovery of consciousness was only correlated with the SON-induced activation in the secondary auditory cortex but not that in the primary auditory cortex.

The prognostic value of SON-MMN shown in the current study was also consistent with previous studies adopting non-self-related stimulus-evoked MMN. However, the previous studies showed a low presence ratio of MMN among patients. For example, Fischer et al. recorded MMN evoked by sine tone in 25% of the patients with DOC [5], whereas Kotchoubey et al. detected MMN in 16% and 31% of their patients (evoked by sine tone and complex tone, respectively) [12]. The detection power was high in the present study—SON-MMN was detected in 7 of 12 patients. Several reasons might explain why SON is effective to evoke an MMN response in patients with DOC. First, SON is known to be a more potent and attention-grabbing stimulus as illustrated by the own-name-effect (for recent review see [14]). Second, the physical properties of SON (deviant stimuli) and sine tones (standard stimuli) differ in many aspects (such as duration and frequency) probably resulting in a comparatively larger amplitude of SON-MMN [23]. Third, familiarity of the SON could enhance the SON-MMN [1]. Maybe so could emotion [7]. Future studies based on a larger sample size are needed in order to directly compare SON-MMN with MMN evoked by non-self-related stimuli for verifying such superiority of SON-MMN statistically.

Our study was the first to adopt MMN evoked by SON in patients with DOC. The presence of SON-MMN in the present study is likely to indicate that the patients retain the brain function that is important for cognitive processing. The protocol in this study employed one Control block to minimize the effects of physical properties and refractoriness factors. However, such a Control condition might have a contextual effect [9] as compared to the targeted Oddball condition. Compared with the vast number of different stimulation features in the Oddball condition, the contextual effect during the Control condition is negligible for SON-MMN since just a minimal

influence may be induced on the brain response to SON. This could be verified by the results from our healthy subjects who showed significant SON-MMN.

In conclusion, our study illustrates that the subject's own name, an emotion relevant self-referential stimulus, is effective to evoke ERP MMN. The small sample size used in the present study prevented us from making general claims about SON-MMN being a reliable marker of self-consciousness, but our empirical data did show potential prognostic values of this novel ERP waveform. Further studies on a larger cohort of patients are warranted to confirm the predictive value of SON-MMN in chronic DOC. Although the present protocol was not designed to detect the special ERPs reflecting self-related processing like Roye et al. [19], future studies in this direction would be valuable for the study of patients with DOC.

## References

[1] M. Beauchemin, L. De Beaumont, P. Vannasing, A. Turcotte, C. Arcand, P. Belin, M. Lassonde, Electrophysiological markers of voice familiarity, Eur. J. Neurosci. 23 (2006) 3081–3086.

[2] J.D. Born, A. Albert, P. Hans, J. Bonnal, Relative prognostic value of best motor response and brain stem reflexes in patients with severe head injury, Neurosurgery 16 (1985) 595–601.

[3] J. Daltrozzo, N. Wioland, V. Mutschler, B. Kotchoubey, Predicting coma and other low responsive patients outcome using event-related brain potentials: a meta-analysis, Clin. Neurophysiol. 118 (2007) 606–614.

[4] H.B. Di, S.M. Yu, X.C. Weng, S. Laureys, D. Yu, J.Q. Li, P.M. Qin, Y.H. Zhu, S.Z. Zhang, Y.Z. Chen, Cerebral response to patient's own name in the vegetative and minimally conscious states, Neurology 68 (2007) 895–899.

[5] C. Fischer, D. Morlet, P. Bouchet, J. Luaute, C. Jourdan, F. Salord, Mismatch negativity and late auditory evoked potentials in comatose patients, Clin. Neurophysiol. 110 (1999) 1601–1610.

[6] J.T. Giacino, K. Kalmar, J. Whyte, The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility, Arch. Phys. Med. Rehabil. 85 (2004) 2020–2029.

[7] K.N. Goydke, E. Altenmuller, J. Moller, T.F. Munte, Changes in emotional tone and instrumental timbre are reflected by the mismatch negativity, Brain Res. Cogn. Brain Res. 21 (2004) 351–359.

[8] I. Holeckova, C. Fischer, M.H. Giard, C. Delpuech, D. Morlet, Brain responses to a subject's own name uttered by a familiar voice, Brain. Res. 1082 (2006) 142–152.

[9] T. Jacobsen, J. Horvath, E. Schroger, S. Lattner, A. Widmann, I. Winkler, Pre-attentive auditory processing of lexicality, Brain Language 88 (2004) 54–67.

[10] T. Jacobsen, E. Schroger, Measuring duration mismatch negativity, Clin. Neurophysiol. 114 (2003) 1133–1143.

[11] B. Kotchoubey, S. Lang, E. Herb, P. Maurer, N. Birbaumer, Reliability of brain responses to the own name in healthy subjects and patients with brain damage,

in: N.C. Moore, M.K. Arikan (Eds.), Brainwaves and Mind: Recent Advances, Kjellberg, Inc., New York, 2004, pp. 75–80.

[12] B. Kotchoubey, S. Lang, E. Herb, P. Maurer, D. Schmalohr, V. Bostanov, N. Birbaumer, Stimulus complexity enhances auditory discrimination in patients with extremely severe brain injuries, Neurosci. Lett. 352 (2003) 129–132.

[13] B. Kotchoubey, S. Lang, G. Mezger, D. Schmalohr, M. Schneck, A. Semmler, V. Bostanov, N. Birbaumer, Information processing in severe disorders of consciousness: vegetative state and minimally conscious state, Clin. Neurophysiol. 116 (2005) 2441–2453.

[14] S. Laureys, F. Perrin, S. Bredart, Self-consciousness in non-communicative patients, Conscious. Cogn. 16 (2007) 722–741.

[15] S. Laureys, F. Perrin, M.E. Faymonville, C. Schnakers, M. Boly, V. Bartsch, S. Majerus, G. Moonen, P. Maquet, Cerebral processing in the minimally conscious state, Neurology 63 (2004) 916–918.

[16] L. Mazzini, M. Zaccala, F. Gareri, A. Giordano, E. Angelino, Long-latency auditory-evoked potentials in severe traumatic brain injury, Arch. Phys. Med. Rehabil. 82 (2001) 57–65.

[17] R. Naatanen, P. Paavilainen, T. Rinne, K. Alho, The mismatch negativity (MMN) in basic research of central auditory processing: a review, Clin. Neurophysiol. 118 (2007) 2544–2590.

[18] F. Perrin, C. Schnakers, M. Schabus, C. Degueldre, S. Goldman, S. Bredart, M.E. Faymonville, M. Lamy, G. Moonen, A. Luxen, P. Maquet, S. Laureys, Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome, Arch. Neurol. 63 (2006) 562–569.

[19] A. Roye, T. Jacobsen, E. Schroger, Personal significance is encoded automatically by the human brain: an event-related potential study with ringtones, Eur. J. Neurosci. 26 (2007) 784–790.

[20] H.V. Semlitsch, P. Anderer, P. Schuster, O. Presslich, A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP, Psychophysiology 23 (1986) 695–703.

[21] M. Signorino, S. D'Acunto, F. Angeleri, P. Pietropaoli, Eliciting P300 in comatose patients, Lancet 345 (1995) 255–256.

[22] W. Staffen, M. Kronbichler, M. Aichhorn, A. Mair, G. Ladurner, Selective brain activity in response to one's own name in the persistent vegetative state, J. Neurol. Neurosurg. Psychiatry 77 (2006) 1383–1384.

[23] R. Takegata, E. Brattico, M. Tervaniemi, O. Varyagina, R. Naatanen, I. Winkler, Preattentive representation of feature conjunctions for concurrent spatially distributed auditory objects, Brain Res. Cogn. Brain Res. 25 (2005) 169–179.

[24] G. Teasdale, B. Jennett, Assessment of coma and impaired consciousness. A practical scale, Lancet 2 (1974) 81–84.

[25] V.J. Wijnen, G.J. van Boxtel, H.J. Eilander, B. de Gelder, Mismatch negativity predicts recovery from the vegetative state, Clin. Neurophysiol. 118 (2007) 597–605.