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Letter to the Editor

Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure

Prediction of clinical outcome of comatose patients remains a major medical, psychological and socio-economical challenge. Neurophysiological probing of residual perceptual abilities in such patients might constitute a promising way to check the functionality of their brains, and to predict their clinical evolution. Indeed, Kane et al. (1993), and more recently Fischer and colleagues (1999, 2004) recorded scalp event-related-potentials (ERPs) in a passive odd-ball paradigm while patients were stimulated with frequent and rare auditory tones. Both studies reported that the presence of a mismatch negativity (MMN)—the first EEG signature of novelty detection (Tiitinen et al., 1994)—predicted awakening, with a strong specificity of 90.9% in the last study.

Here, we report the MMN results of the first 30 comatose patients (coma Glascow score <8) recorded at bedside in a neuro-intensive care unit. We prospectively recorded patients suffering from various causes of coma: subarachnoïd hemorrhage with arterial vasospasm (11), severe head trauma (6), brain hematoma (5), ischaemic stroke (4), tumor (2) and meningoencephalitis (2). All patients were free from any sedative drugs for more than 4 days. Delay between coma onset and ERP recordings ranged from 4 to 96 days (median = 25 days; mean = 26.9 days). Age ranged from 19 to 70 years (median = 47; mean = 47.8).

Binaural tones were pseudo-randomly delivered (+80 dBl, 40 ms duration, frequent at 1 kHz in 85% of trials, rare at 2 kHz in 15% of trials) every 1000 ms. Our paradigm uses 200 rare stimulations. The P8 Medatec system (Bruxelles, Belgium) was used to deliver the acoustic stimulation, to record and digitize the EEG at 500 Hz from Cz referenced to the left mastoid, to filter the signal (Time Constant = 0.05 s; Low-pass cutoff = 20 Hz) and to automatically select artefact free trials. Individual trials were then exported and processed in Matlab 6.5 (Natick, MA) to reject frequent trials occurring immediately after a rare trial, to average the signal and to perform sample-by-sample t tests, with a criteria of a minimum of 5 consecutive P values lower than 0.05. Only recordings in which we could observe a P1/N1 complex followed by a significant MMN were considered as MMN positive.

We then evaluated clinical outcome at 1 month after ERP recordings with the Glascow Outcome Scale (GOS), and compared the MMN+ and MMN− groups. Negative outcome included GOS scores of 1 or 2 (vegetative state or dead), while positive outcome included scores corresponding to conscious states (from 3 to 5).

Across our 30 patients, 10 (33%) had a MMN (see Fig. 1). Nine of these patients eventually awakened (90%), while the last one died from an unrelated event which occurred 14 days after ERP recordings. This patient was affected initially with a left middle cerebral artery ischaemic stroke due to infectious vascularitis in the context of a left hemispheric bacterial brain abscess. He then presented a second stroke in the vertebro-basilar territory. Within the MMN negative group, 13 patients died or evolved to a vegetative state (65%), while 7 of them (35%) awakened. These results mean that in our study, MMN predicted awakening with a specificity of 93%, a sensitivity of 56%, and with a positive predictive value of 90%. Age (49.5 years for MMN+ group vs 45.6 years for MMN− group) and delay between coma onset and ERP recordings (29 days for MMN+ group vs 25 days for MMN− group) were similar between groups (both P values >0.6 in Student t tests). Causes of coma were distributed similarly between the two groups (χ^2 test P value = 0.8).

Our data closely replicate Fischer and colleagues results, and therefore confirm the usefulness of bedside recording of auditory ERPs to assess residual cognitive integration of current environmental stimuli in various neurological disorders (Naccache et al., 2004), and to predict awakening in comatose patients. Moreover, our approach is easier than the one used by Fischer and colleagues, and necessitates a comparable duration (23.5 min in our case compared to 14–38 min). The simple and automatized EEG signal processing adopted here offers a result within a few minutes. In spite of this simplicity, this methodology enables the recording of sufficient trials to obtain individual statistically significant results. Therefore, we think that this reliable method might be adopted by a large set of Intensive Care units in order to flexibly evaluate current level of cognitive integration of comatose patients, to evaluate the dynamic impact of sedative drugs, and to predict their clinical outcome.

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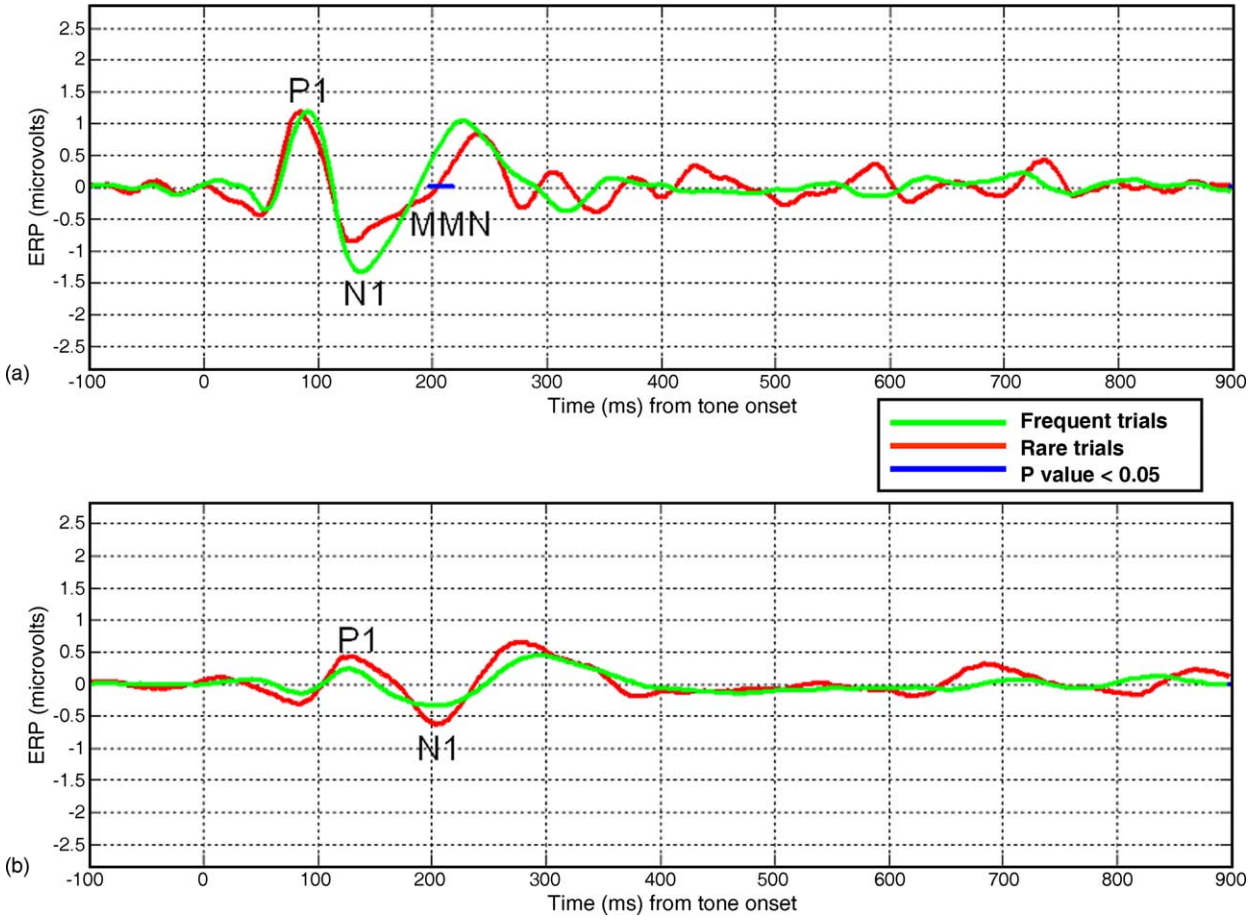

Fig. 1. Auditory cognitive ERPs of two comatose patients. The upper graph (a) shows ERPs of a patient from the MMN positive group. After an initial P1/N1 complex similar for rare (red) and frequent (green) tones, ERPs show a significant divergence the polarity (rare minus frequent is negative) and the latency (around 200 ms) of which correspond to the MMN. The lower graph (b) shows ERPs of a patient from the MMN negative group. The initial P1/N1 complex is still present, but delayed and small in amplitude. No significant difference could be observed between rare tones ERPs and frequent tones ERPs during the whole epoch of analysis.

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