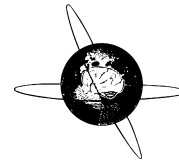




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Mismatch negativity predicts recovery from the vegetative state

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Abstract

Objective: Mismatch negativity (MMN) is an automatic event related brain response, well investigated in the acute phase after severe brain injury: the presence of a MMN is often found to predict the emergence from coma, and the exclusion of shifting into a vegetative state (VS). In the present study MMN was examined during recovery from VS.

Methods: Ten vegetative patients were repeatedly examined every 2 weeks for an average period of 3.5 months. Amplitudes and latencies were related to the patients' recovery from VS to consciousness, and to a healthy norm group. In addition, MMN was examined on its prognostic value in VS patients, in predicting recovery to consciousness and long-term functional outcome.

Results: With recovery to consciousness MMN-amplitudes increased. A sudden increase was seen in MMN amplitude when patients started to show inconsistent behavioural responses to simple commands. At this level MMN resembled the MMN response as was seen in the norm group. In addition, the MMN-amplitude and latency during the first measurement predicted the patients' outcome on recovery to consciousness.

Conclusions: With recovery from VS to consciousness the ability to process auditory stimulus deviance increases. A sudden enhancement in MMN-amplitude preceded overt communication with the environment. This might be indicative of the consolidation of neural networks underlying overt communication. Moreover, MMN can be helpful in identifying the ability to recover from VS.

Significance: MMN can be used to track recovery from the vegetative state in the post-acute phase after severe brain injury. In addition, MMN can be used to predict the ability to recover from the vegetative state.

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Keywords: Mismatch negativity; Vegetative state; Minimally conscious state; Consciousness

1. Introduction

Severe brain injury results in high morbidity and mortality rates. The majority of patients experience long-term or lifelong disabilities, bringing along major costs for family and society. So far there has been limited research concerning the group of young adults, who have the highest risks (Jennett, 1996; Finfer and Cohen, 2001).

Many individuals who sustain severe acquired brain injury experience prolonged or permanent disorders of con-

sciousness. Acute severe brain injury inevitably results in coma, a state of loss of consciousness with the eyes closed, with no sleep–wake cycle (Multi-Society Task Force on Persistent Vegetative State, 1994a). If not resulting in death within a period of 3 to 4 weeks, this coma will develop into a vegetative state (VS, Jennett and Plum, 1972), where the patient seems awake but not aware: uncommunicative and unresponsive to the environment. VS is defined as persistent (PVS) as presence for longer than a month (Bernat, 2006). If recovery continues, patients regain minimal responsiveness to external stimuli (minimally conscious state, MCS) (Giacino et al., 2002), that eventually may result in full recovery of consciousness and responsiveness.

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Otherwise, patients may remain for a long time, or even the rest of their life span, in a vegetative or minimally conscious state. In a later stage it may be considered permanent although on clinical rather than temporal considerations (Working Party of the Royal College of Physicians, 2003). Once this diagnosis has been made, ethical and legal issues around withdrawal of treatment may arise (Jennett, 2005). The current study focuses on patients who were in VS for at least a month.

In general, 1–14 percent of the traumatic, and 12 percent of the non-traumatic prolonged comatose patients shift into VS (Multi-Society Task Force on Persistent Vegetative State, 1994a,b). Fifty-two percent of the traumatic and 15 percent of the non-traumatic vegetative patients do recover to consciousness (Multi-Society Task Force on Persistent Vegetative State, 1994b). Since recovery from VS to consciousness does occur and depends on residual brain capacities, longitudinal research in the post-acute phase within this group is of great importance to understand what underlies.

The diagnosis of VS and MCS is based on clinical observation of behavioural criteria mostly. Several uncertainties stick to this method. First, observational methods depend on the subjective interpretation of behavioural responses, while conscious experience often occurs without behavioural signs. Second, no initial behavioural differences exist between the patients who may recover to consciousness and those who remain permanently vegetative.

To obtain complementary objective information about the level of consciousness in non-responsive patients, the present study focuses on neurophysiological responses during the recovery from VS to consciousness. A longitudinal study was performed in which the Mismatch Negativity (MMN) (Näätänen et al., 1978) was examined.

MMN is generated by the brain's automatic response to physical stimulus deviation from the preceding stimulus in repetitive auditory input, revealing that physical features of auditory stimuli are fully processed regardless whether they are attended to or not (Näätänen et al., 2004). Mismatch negativity has repeatedly shown to predict outcome after coma (Fischer et al., 1999, 2004; Kane et al., 1993, 1996; Luauté et al., 2005; Morlet et al., 2000). Fischer et al. (1999, 2004) demonstrated that in the acute phase the presence of MMN predicted the exclusion of shifting into PVS. Additionally, Luauté et al. (2005) showed that when MMN was present in comatose patients no patient turned to permanent VS 1 year after the brain insult. MMN responses have been found in VS and MCS patients, especially when complex tones or musical notes were used (Jones et al., 1994; Kotchoubey et al., 2003, 2005). Additionally, in the study of Kotchoubey et al. (2005) 6 months after the brain insult clinical improvement was observed more frequently in VS and MCS patients with a significant MMN than in those without the MMN. Up to now researchers have not longitudinally investigated MMN responses during the recovery from VS. The present study reports on longitudinal changes in MMN responses during recovery to consciousness, and on its prognostic value in VS patients.

2. Methods

2.1. Participants

Ten severely brain-injured patients (7 were male; age $M = 17.3$, $SD = 4.4$, 8–25 years), who were admitted to an Early Intensive Neurorehabilitation Programme (Eilander et al., 2005), took part in the study between November 2002 and January 2004. The duration of the patients' participation in the programme ranged from 1.5 to 5.2 months ($M = 3.5$ months; $SD = 1.03$) (Table 1). Time since injury at admission ranged from 6.2 to 19.4 weeks ($M = 11.6$ weeks; $SD = 3.6$). All but two patients suffered from a traumatic brain injury caused by traffic accidents (see Table 1 for patients' details).

A norm group consisted of 16 persons, matched for mean age ($P = 0.6$) and gender (56% were male).

All the patients and the norm group participated in this study following informed consent given by one of the parents or a legal representator (all the patients and norm group aged < 16 years), or by themselves (norm group aged ≥ 16). The study has been approved by a medical Ethics Committee (METTOP).

2.2. Level of Consciousness

For the Level of Consciousness (LoC) a categorisation was used based on the definitions described by 'the International Working Party on the Management of the Vegetative State' (Andrews, 1996), and the Aspen Neurobehavioural Conference (Giacino et al., 1997). The categorisation describes a comatose state, three vegetative sub-states, three non-vegetative sub-states, and a conscious state (see Table 2 for the classification scheme in detail).

This classification scale showed high reliability and validity (Eilander, submitted). The interrater-reliability (Spearman's rho) varies between 0.85 and 0.94. The interrater-agreement (Cohens' weighted Kappa) varies between 0.90 and 0.95. The intrarater-reliability is 0.96 and the intrarater-agreement is 0.94. Correlation of the scores of the rated scores with the Western Neuro Sensory Stimulation Profile (WNSSP) (Ansell et al., 1989) varies between 0.85 and 0.90, and with the Disability Rating Scale (DRS) (Rappaport et al., 1982) between 0.88 and 0.94.

In a second approach this classification was reduced to four levels: level 1 was defined as Coma, the levels 2, 3, and 4 as VS, levels 5 and 6 as MCS, and levels 7 and 8 as exitMCS (5, 6) or Conscious State.

2.3. MMN data acquisition and analysis

The presented stimuli were 1500 pure tones of 1000 Hz (85%, standard) and 1500 Hz (15%, deviant), with an intensity of 70 dB SPL and duration of 75 ms (rise and fall time 10 ms), delivered binaurally through insert earphones. The interstimulus interval was 500 ms. Electroencephalographic

Table 1
Patients' details

P	Ms	TM	M/ F	Age	Cause	Initial CT-scan (s)*	GCS	T1	T2	T3	LoC1	LoC2	LoC- discharge	LOCT- discharge	DRS	GOSE	Toutcome
1	2	6.5	M	17.6	Traffic accident	Epidural haematoma (right)	2t	72	80	139	4	4	4	217	3	3	3.0
2	4	6.1	M	15.4	Traffic accident	Skull fractures, arachnoid haemorrhages, contusion and punctual haemorrhages (right frontal, temporal, parietal), diffuse swelling	4	33	136	112	5	5	5	204	4	3	2.9
3	3	2.4	M	25.2	Traffic accident	Skull fracture, oedema and punctual haemorrhages (cortical), diffuse swelling, and diffuse white matter lesions	2t	65	64	77	4	7	8	141	6	3	2.7
4	4	2.9	M	8.4	Cerebral haemorrhages	Intraventricular and intracerebral haemorrhages, left cortical	2t	33	81	119	3	7	7	133	7	3	2.6
5	8	1.9	F	18.8	Traffic accident	Oedema, ischemia, high intracranial pressure, diffuse swelling	3	29	49	115	4	7	8	164	4	3	2.4
6	3	4.5	M	17.5	Traffic accident	Oedema, intraventricular and intracerebral haemorrhages, focal lesions (subcortical, brainstem), diffuse white matter lesions	4	13	44	92	4	4	8	136	7	6	2.5
7	7	2.6	M	21.8	Traffic accident	Punctual haemorrhages, intraventricular haemorrhage (left), diffuse swelling, diffuse axonal injury	5	26	71	105	4	4	4	176	3	3	2.5
8	5	2.2	F	15.7	Traffic accident	Subarachnoid haemorrhage (right), high intracranial pressure, oedema (right subcortical and brainstem)	4	30	60	99	3	5	8	159	5	3	2.4
9	9	2.9	M	17.2	Traffic accident	Intraventricular haemorrhages (bilateral), multiple punctual haemorrhages, Large haemorrhage in basal ganglia, and right frontal, oedema (mainly left periventricular white matter)	3	62	80	157	3	5	5	237	1	1	2.2
10	4	3.6	F	15.2	Pneumonia + sepsis shock	Hypodensity in basal ganglia and cortical temporoparietal, anoxia, cortical and cerebellar atrophy, diffuse white matter lesion	3	57	102	45	3	2	3	147			2.7

P, patient; Ms, participated measurements; TM, time between injury and first measurement in months; F, female; M, male; Age, age at injury; *, diagnoses based on the medical reports of the acute phase; GCS, GCS at admission hospital; t, endotracheal tube; T1, time at ICU in days; T2, time before admission RCL in days; T3, programme duration RCL in days; LoC1, Level of Consciousness during the first EEG-protocol; LoC2, Level of Consciousness during the last EEG-protocol; LoC-discharge, Level of Consciousness at discharge; LoCT-discharge, time after injury in days for Level of Consciousness at discharge; DRS, Disability Rating Scale; GOSE, Glasgow Outcome Scale extended; Toutcome, time after injury in years for DRS and GOSE.

Table 2
Levels of Consciousness (LoCs)

Global level	Score	Description of the levels
Coma		<i>Eyes are closed all the time. No sleep–wake cycles present.</i>
	1	All major body functions such as breathing, temperature control, or blood pressure can be disturbed. Generally, no reactions are noticed after stimulation. Sometimes reflexes (stretching or flexing) can be observed as a reaction when strong pain stimuli have been applied. No other reactions present.
Vegetative State (VS)		<i>Patient has some sleep–wake cycles, but no proper day–night rhythm. Most of the body functions are normal. No further ventilation is required for respiration.</i>
	2	Very little response (hypo-responsive) Generally no response after stimulation. Sometimes delayed presentation of reflexes is observed.
	3	Reflexive state Often stimuli result in massive stretching or startle reactions, without proper habituation. Sometimes these reactions evolve into massive flexing responses. Roving eye movements can be seen, without tracking. Sometimes grimacing occurs after stimulation.
	4	High active level and/or reactions in stimulated body parts Generally spontaneous undirected movements. Retracting a limb following stimulation. Orienting towards a stimulus, without fixating. Following moving persons or objects, without fixating.
Minimally Conscious State (MCS)		<i>Patient remains awake most of the day.</i>
	5	Transitional state Following and fixating of persons and objects. Generally more directed reactions to stimuli. Behaviour is automatic, i.e. opening of the mouth when food is presented, or reaching towards persons or objects. Sometimes emotional reactions are seen such as crying or smiling towards family or to specific (known) stimuli.
	6	Inconsistent reactions Sometimes, but not always, obeying simple commands. Totally dependent. Patient has profound cognitive limitations; neuropsychological testing is impossible. Level of alertness is fluctuating, but in general low.
	7	Consistent reactions Patient obeys simple commands. The level of alertness is high and stable. Many cognitive disturbances remain. Patient is totally dependent.
Consciousness	8	Patient is alert and reacts to his/her environment spontaneously. Functional understandable mutual communication is possible, sometimes with technical support. As yet, cognitive and behavioural disturbances can be present.

activity (EEG, sampling rate 2 kHz, Common Mode Rejection Ratio >80 dB) was recorded (BioSemi activeTwo, Amsterdam) using actively shielded electrodes. The total equipment was tested and approved as regards safety by a Metron QA-90 safety tester in the Tweesteden Hospital (Tilburg, The Netherlands). The electrodes were placed using an EEG-head cap and electrode gel (Parker Signa) according to the 10/20 system, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz, referenced to linked mastoids. Many studies have used the tip of the nose as a reference for recording the MMN, but we anticipated that placing an electrode on the nose could evoke defensive behaviour (e.g., grabbing the nose electrode) in some of the patients participating in the study. Secondly, a linked mastoid reference was needed for other measurements taken from the same patients (see above).

Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from electrodes placed on the infraorbital and supraorbital regions of the two eyes in line with the pupil. EOG artefacts were corrected using a regression procedure (Gratton et al., 1983).

EEG signals were band-pass filtered (0.15–30 Hz, 48 dB/octave). The raw data were segmented into 1500 epochs, including a 100 ms prestimulus baseline. Epochs with an

amplitude change exceeding $\pm 100 \mu\text{V}$ at any channel were automatically rejected. ERPs were averaged separately for the standards and deviants. The ERP to standards included the responses to those standards which immediately followed deviants.

After averaging the standard and deviant responses for each measurement and subject the ERPs were filtered between 3 and 30 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject it was visually inspected whether there was a N1 in both averaged standard and deviant responses. Difference waveforms were computed by subtracting the averaged ERP elicited by the standard from that of the deviant, and were filtered between 3 and 8 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject MMN was defined as being any negativity differing from zero level within the time window of 100–300 ms.

2.4. Definition of outcome

When the patients were discharged from the programme their LoC was determined by the rehabilitation physician, based on the description in Table 2, after a discussion with the multidisciplinary treatment team about each patient (see Table 2). This LoC is further referred to as LoC_{discharge}.

2.5. Long-term outcome: Disability Rating Scale (DRS) and Glasgow Outcome Scale extended (GOSE)

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982) as well as the GOSE (Wilson et al., 1998) were administered. The DRS consists of eight items, which can be summed up to values from 0 to 29. A high score on an item indicates a low level of functioning on that aspect. To make the two scales more comparable, the DRS was reduced to 8 categories according to Rappaport et al. (1982): 1 = dead (score 30), 2 = vegetative state (score 22–29), 3 = extremely severe disabled (score 17–21), 4 = severely disabled (score 12–16), 5 = moderately severe disabled (score 7–11), 6 = moderately disabled (score 4–6), 7 = mildly to partially disabled (score 1–3), and 8 = no disability (score 0).

The GOSE is a one-item rating scale including eight outcome categories and can be administered through a structured interview (Wilson et al., 1998). Outcome categories are: 1 = death, 2 = vegetative state, 3 = lower severely disabled, 4 = upper severely disabled, 5 = lower moderately disabled, 6 = upper moderately disabled, 7 = lower good recovery, 8 = upper good recovery.

2.6. Experimental procedure

Nine days after a patient was admitted to the programme the first measurements took place. Patients were examined while they were lying in a bed in a quiet room with a constant temperature ($23 \pm 1^\circ\text{C}$). Every 2 weeks the MMN measurement was performed at the same time of the day (between 10:30 a.m. and 11:30 p.m.), as part of an ERP protocol. Brainstem auditory evoked potentials (BAEPs) were also recorded, and they were present in all of the measurements of each subject. In the same week the rehabilitation physician determined LoC.

These assessments were performed until the patient was discharged: (a) a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities, or (b) a patient did not show any recovery in a period of at least 6 weeks during the programme.

The norm group was measured once, in the same position and location, at different times of the day. They underwent the same EEG-protocol as the patients.

Long-term outcome was determined by the DRS and GOSE scores at least 2 years after the injury ($M = 2.6$, $SD = 0.28$, see Table 1 for the exact time intervals: Outcome). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

2.7. Statistical analysis

The longitudinal changes of MMN-amplitude, and MMN-peak latency were analysed as a function of LoC using a linear Mixed Model procedure. LoC and the individual subjects were included as random factors. Mixed-effects

models use all available data, can properly account for correlation between repeated measurements on the same subject, have large flexibility to model time effects, and can handle missing data appropriately (Francis et al., 1991; Keselman et al., 2001). Mixed-effects models can be used to model data of ordinal level (Gueorguieva and Krystal, 2004).

Mann–Whitney two independent samples tests were used to examine the ‘between group effects’ for the patient group in the different LoCs and the norm group.

Finally, the predictive value of MMN-amplitude and MMN-peak latency for outcome was examined, using linear regression analyses and Receiver Operating Characteristic (ROC) analyses.

3. Results

3.1. Behavioural indices of recovery

At admission, the patients’ averaged LoC score was 3.6 (± 0.52). At the end of the programme the average LoC score had increased to 5.9 (± 1.9). Five patients reached a conscious level (exit MCS: LoC 7 or 8), 2 patients were still in MCS (LoC 5 or 6), and 3 patients were still in VS (LoC 2–4) at the end of the programme (see Table 1 for LoC_{discharge}).

The long-term outcome scores on the DRS and GOSE could be obtained for 9 patients, and are shown in Table 1. Two to 3 years after the injury the mean score on the DRS was 4.4 (± 2.0). The mean score on the GOSE was 3.1 (± 1.3).

3.2. Changes in MMN: longitudinal measurements

Fig. 1 shows the MMN-amplitude as a function of LoC when the 8 sublevels were taken into account. With an increasing LoC, the MMN-amplitude became larger, showing a discontinuous pattern over LoCs, $F(5, 26) = 6.6$, $P < 0.0001$. A sudden increase in MMN amplitude occurred after LoC5. Fig. 2 shows the accompanying grand averages.

When LoC was divided into three levels (VS, MCS, exit MCS) a significant increase of MMN amplitude was found when patients recovered from the VS to consciousness, $F(2, 22) = 7.32$, $P = 0.004$ (Fig. 3).

Although MMN-peak latency decreased with recovery, these effects were not significant, both when LoC was divided into 8 and 4 sublevels (respectively, $F(5, 36) = 1.07$, $P = 0.40$, $F(2, 38) = 1.75$, $P = 0.20$).

3.3. Comparison with the norm group

Group effects for LoC 1, 2 and 8 could not be statistically analysed. No patients were scored at LoC 1 during this study. Only one patient was measured twice in LoC 2, and no patients were measured in LoC 8 (see Table 3 for group

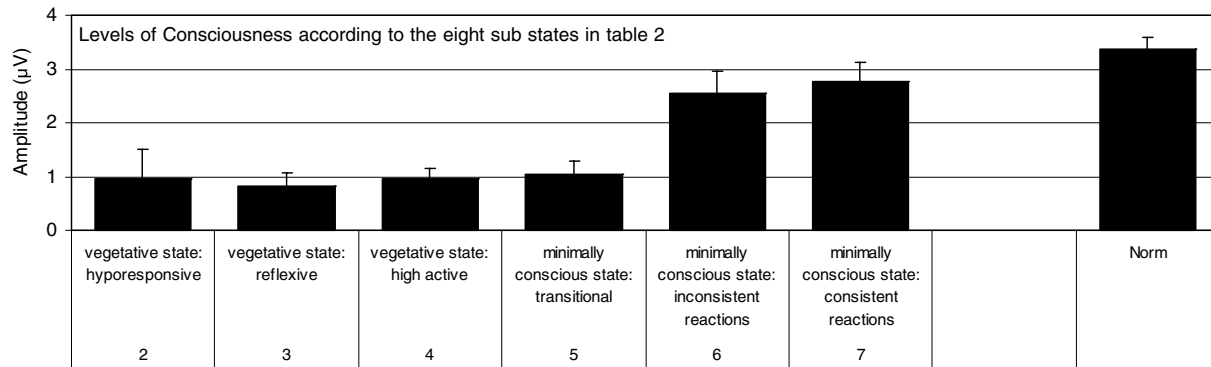


Fig. 1. Longitudinal measurements: mean MMN-amplitude (Fz) and standard error for each Level of Consciousness according to the levels in Table 2 versus the norm group. For number of measurements see Table 3.

means and standard deviations). Therefore, analyses were only performed for LoC 3–LoC 7.

MMN-amplitude within each LoC in the patient group was compared with the MMN in the norm group. Group effects were found for MMN-amplitude. Amplitudes in LoC 3 to 5 were smaller in comparison to the norm group (respectively, $U = 2.0$, $P < 0.0001$; $U = 1.0$, $P < 0.0001$; $U = 2.0$, $P = 0.002$), whereas LoC 6 and 7 did not significantly differ from the norm (respectively, $U = 6.0$, $P = 0.21$; $U = 10.0$, $P = 0.14$). When LoC was divided into four levels (Coma, VS, MCS, and exit MCS) the patients' MMN-amplitude in VS and MCS significantly differed from the norm group (respectively, $U = 3.0$, $P < 0.0001$; $U = 8.0$, $P = 0.002$). Patients who emerged from MCS did not significantly differ from the norm group any longer ($U = 10.0$, $P = 0.14$).

Patients' peak latencies at LoC 3 and 5 differed (marginally) from the norm group (respectively, $U = 17.0$, $P = 0.06$; $U = 9.0$, $P = 0.03$). No differences were found

between the norm group and patients at LoC 4, 6, and 7 (respectively, $U = 44.0$, $P = 0.53$; $U = 11.0$, $P = 0.55$; $U = 19.0$, $P = 0.63$). When LoC was divided into four levels (Coma, VS, MCS, and exit MCS) the patients' MMN latency in VS marginally differed from the norm group ($U = 61.0$, $P = 0.06$). Patients in MCS and patients who emerged from MCS did not significantly differ from the norm group any longer (respectively, $U = 30.0$, $P = 0.2$; $U = 19.0$, $P = 0.63$).

3.4. Predictive value of MMN: relation of the first measurement to outcome

MMN-amplitude during the first measurement strongly predicted $LoC_{discharge}$ ($\beta = -0.94$, $t = -8.07$, $P < 0.0001$). The patients with $LoC_{discharge} < 7$ showed smaller MMN amplitudes during their first measurement, and the patients who recovered to $LoC_{discharge} = 7$ or 8 showed larger MMN amplitudes during their first measurement. The

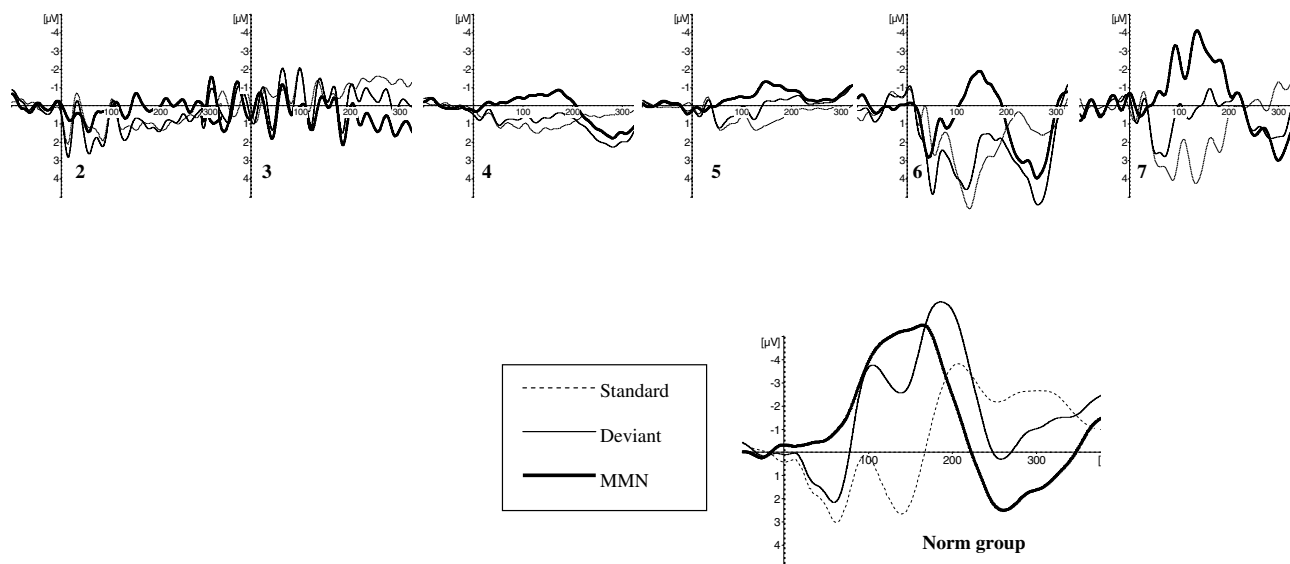


Fig. 2. Grand averages of MMN (Fz-linked Mastoids, 0.15–30 Hz, 48 dB/octave) for each Level of Consciousness according to the levels in Table 2 versus the norm group. Potentials related to the standard stimuli, potentials related to the deviant stimuli, and the MMN (difference between the deviant and standard).

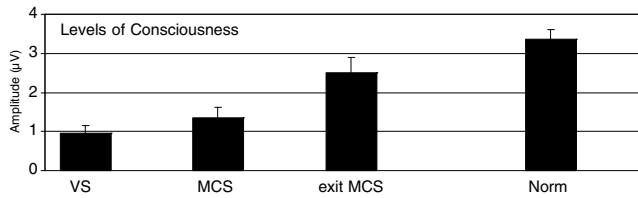


Fig. 3. Longitudinal measurements: mean MMN-amplitude (Fz) and standard error for Level of Consciousness when divided into three levels: VS, MCS, and exit MCS.

LoC score during the first measurement did not predict LoC_{discharge} ($P_s > 0.40$) (Table 4).

A ROC analysis for MMN amplitude at the first measurements showed 100% sensitivity and specificity in predicting outcome at the end of EINP, when a cut-off value of LoC_{discharge} < 7 was used ($P = 0.009$).

Regression analyses did not show significant results for MMN-amplitude during the first measurement in predicting the long-term outcome for DRS and GOSE ($P_s > 0.10$). However, the occurrence of MMN amplitude larger than $-1 \mu\text{V}$ predicted the DRS score about 2 years after the injury ($P = 0.02$).

See Fig. 4 for the distribution of the patients' first MMN-amplitude compared to their short-term and long-term outcome.

In comparison with the amplitude, a less strong prediction was shown for the initial MMN-peak latency for LoC_{discharge} ($\beta = -0.67$, $t = -2.58$, $P = 0.03$) (Table 4). Shorter peak latencies were found in the patients who recovered to higher LoC scores. In addition, the ROC analysis for MMN-peak latency showed less strong sensitivity and specificity in predicting outcome at the end of EINP ($P = 0.02$). No significant results were found for latency during the first measurement in predicting the long-term outcome for DRS and GOSE ($P_s > 0.10$).

4. Discussion

MMN-amplitude predicted the level of consciousness, and functional outcome 2 years after the injury. All

Table 3
Means and standard deviations (in parentheses): peak latency and peak amplitude of MMN (Fz) for each level of consciousness and the norm group

LoC	Measurements	Patients	Latency (ms)	Amplitude (µV)
1 ^a	0	0		
2	2	1	204 (64)	-0.9 (0.7)
3	9	5	201 (42)	-0.8 (0.5)
4	18	7	196 (64)	-0.9 (0.7)
5	12	4	197 (50)	-1.0 (0.7)
6	3	2	153 (12)	-2.7 (0.5)
7	4	3	141 (23)	-2.9 (1.0)
8 ^a	0	0		
Norm		16	155 (23)	-3.4 (1.1)

^a No measurements were performed during these levels of consciousness.

Table 4
MMN-peak amplitude, peak latency and LoC during the first measurement, and LoC at discharge of the programme

Patient	LoC _{first}	MMN _{first}		LoC _{discharge}
		Amplitude (µV)	Latency (ms)	
1	4	-0.19	248.54	5
2	5	-0.40	251.95	5
3	4	-1.46	156.25	8
4	3	-1.29	173.34	7
5	4	-2.11	154.30	8
6	4	-1.70	168.95	8
7	4	-0.34	399.41	4
8	3	-1.59	228.52	8
9	3	-0.86	208.50	5
10	3	-0.32	238.28	3

patients who ultimately recovered to consciousness already showed higher amplitudes and shorter latencies in VS (first measurement) in comparison to the patients who remained in VS or MCS. A less strong prognostic value was found for the long-term functional outcome. The DRS and GOSE scores reveal that most of the conscious patients were still severely disabled about 2 years after their injury.

Another striking result was the increased MMN that was demonstrated during the period leading up to the recovery of consciousness. Amplitudes became larger, and reached the healthy levels of a matched norm group. The difference between the patients' states according to electrophysiological data did not exactly correspond to the clinical diagnosis, that is VS versus MCS. Rather, the most important improvement of the electrophysiological status is within the range of minimally conscious states. A sudden increase in MMN occurred within MCS (from LoC 5–LoC 6) and preceded overt consistent behavioural responses to the environment (LoC 7). Unfortunately, practical issues (discharged from the programme, behavioural problems) lead to the fact that no patients were measured in LoC 8.

Our results on the predictive value of MMN extend the previous results of Fischer et al. (2004) in the acute phase. In their study MMN was found to predict the awakening from coma and the exclusion of VS. The present study reveals that MMN can give insight in those patients who do shift in to VS: MMN predicts the recovery from VS to consciousness.

Previous studies already showed residual cerebral function in severely brain-injured patients (Boly et al., 2004; Laureys et al., 2000; Schiff et al., 2002). Differences were found between VS and MCS patients in auditory processing (Boly et al., 2004). Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed more significant activity in superior and middle temporal gyri and tighter functional connectivity with other brain areas in MCS patients than was found in patients in VS while they were exposed to auditory stimulation. In addition, some prefrontal activation was shown in MCS patients in a language related task (Schiff et al., 2002).

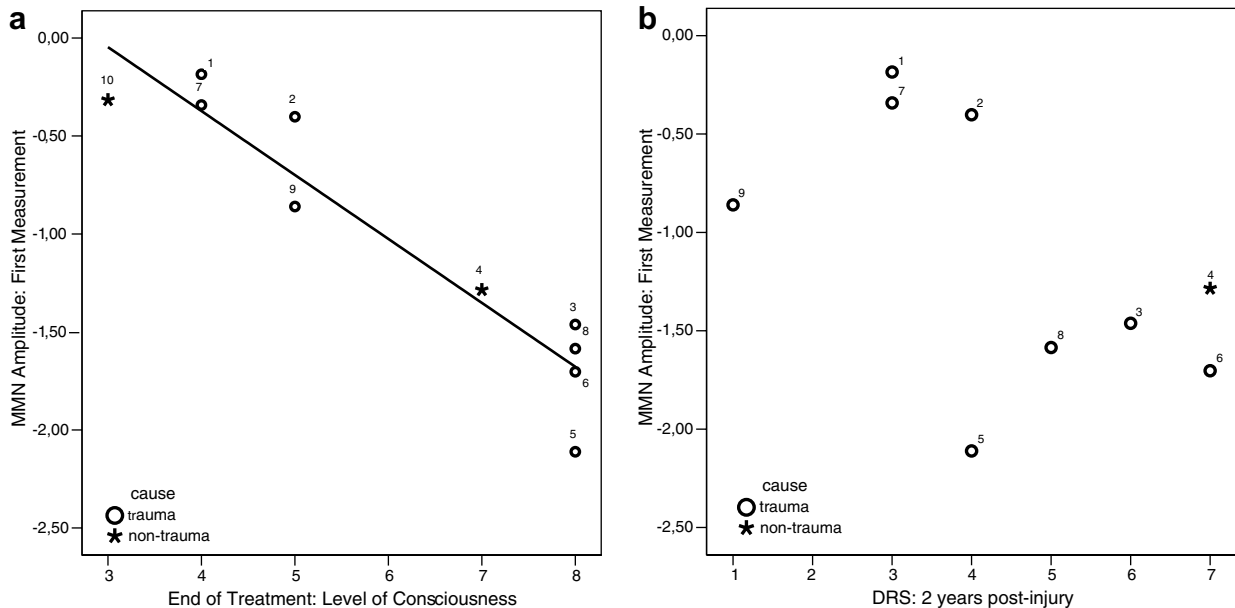


Fig. 4. Predictive value of MMN-amplitude during the first measurement: (a) Level of Consciousness at the end of the treatment programme. (b) Disability Rating Scale.

The PET and fMRI results demonstrated a consistent language-responsive network while the patients showed inconsistent evidence of receptive and expressive language skills. These same regions were earlier found to be involved in the generation of MMN using a topographic event related potential study (Giard et al., 1990). The emergence from MCS is defined by showing reliable and consistent interactive communication or functional use of objects (Giacino et al., 2002; Schiff and Purpura, 2002). The clear enhanced MMN found in our patient group in LoC 6 might therefore be indicative for the consolidation of neural networks underlying consistent interactive communication. This result confirms earlier findings in which neural activity expressed in MMN preceded behavioural learning using a speech related MMN paradigm (Tremblay et al., 1998). Some learning occurs at a pre-attentive level, and therefore can be assessed in the absence of behavioural responses.

In conclusion, we showed that MMN is a powerful tool in predicting the recovery from VS to consciousness. However, a larger patient group is needed to elaborate on these findings. We recommend that in future studies other possibly important predictors of outcome are incorporated, such as clinical, demographical, and psychological information. The predictive value of the MMN may strongly depend on such other variables. Another recommendation for future studies is to study long-term functional outcome of these patients. This will reveal whether early recordings of the MMN predict long-term outcome as well. In addition, in such future studies a nose reference might be a good choice for recording the MMN, as opposed to linked mastoids used here (Näätänen et al., 2004; Schröger, 1998). As outlined in Section 2, we were faced with practical constraints in our choice of linked mastoids as a reference.

Our results add to the knowledge on differences between and within VS and MCS. The sudden increase in MMN within MCS points out that the eight sublevels of consciousness we used could be of additional information, and that VS and MCS are not static states.

A speech related, topographical MMN study is important to confirm the enhanced MMN amplitude to be preceding overt communication with the environment. A combination of structural and functional assessment (fMRI, PET, ERP) of information processing using words or vowels (Kotchoubey et al., 2001; Kotchoubey et al., 2005) in a longitudinal design might give more insight.

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References

Andrews K. International working party on the management of the vegetative state. *Brain Inj* 1996;10:797–806.

- Ansell BJ, Keenan JE, de la Rocha O. Western Neuro Sensory Stimulation Profile; a tool for assessing slow-to-recover head-injured patients. Tustin, California: Western Neuro Care Centre, 1989;24.
- Bernat JL. Chronic disorders of consciousness. *Lancet* 2006;367:1181–92.
- Boly M, Faymonville M-E, Peigneux P, Lambermont B, Damas P, Del Fiore G, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol* 2004;61:233–8.
- Eilander HJ, Wijnen VJM, Scheirs JGM, De Kort PLM, de Prevo AJH. Children and young adults in a prolonged unconscious state due to severe brain injury: outcome after an early intensive neurorehabilitation programme. *Brain Inj* 2005;19:425–36.
- Eilander HJ, van de Wiel M, Wijers M, van Heugten CM, Buljevac D, Lavrijsen JCM, et al. The reliability and validity of the PALOC-s: A Post-Acute Level of Consciousness scale for assessment of patients with prolonged disturbed consciousness after brain injury. Submitted.
- Finfer SR, Cohen J. Severe traumatic brain injury. *Resuscitation* 2001;48:77–90.
- Fischer C, Morlet D, Bouchet P, Luauté J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol* 1999;110:1601–10.
- Fischer C, Luauté J, Adeleine P, Morlet D. Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology* 2004;63:669–73.
- Francis DJ, Fletcher JM, Stuebing KK, Davidson KC, Thompson NM. Analysis of change: modeling individual growth. *J Consult Clin Psychol* 1991;59:27–37.
- Giacino JT, Zasler ND, Katz DI, Kelly JP, Rosenberg JH, Filley CM. Development of practice guidelines for assessment and management of the vegetative and minimally conscious states. *J Head Trauma Rehabilitation* 1997;12:79–89.
- Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state. Definition and diagnostic criteria. *Neurology* 2002;58:349–53.
- Giard MH, Perrin F, Pernier J, Bouchet P. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. *Psychophysiology* 1990;27:627–40.
- Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983;55:468–84.
- Georguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry* 2004;61:310–7.
- Jennett B. Historical perspective on head injury. In: Narayan RK, Wilberger JE, Povlishock JT, editors. *Neurotrauma*. New York: McGraw-Hill Companies; 1996. p. 3–11.
- Jennett B. Part I: definitions, diagnosis, prevalence and ethics. *Neuropsychol Rehabil* 2005;15:163–5.
- Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1972;734–7.
- Jones R, Hux K, Morton-Anderson KA, Knepper L. Auditory stimulation effect on a comatose survivor of traumatic brain injury. *Arch Phys Med Rehabil* 1994;75:164–71.
- Kane NM, Curry SH, Butler SR, Cummins BH. Electrophysiological indicator of awakening from coma. *Lancet* 1993;341:688.
- Kane NM, Curry SH, Rowlands CA, Manara AR, Lewis T, Moss T, et al. Event-related potentials – neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med* 1996;22:39–46.
- Keselman HJ, Algina J, Kowalchuk RK. The analysis of repeated measures designs: a review. *Br J Math Stat Psychol* 2001;54:1–20.
- Kotchoubey B, Lang S, Baales R, Herb E, Maurer P, Mezger G, et al. Brain potentials in human patients with extremely severe diffuse brain damage. *Neurosci Lett* 2001;301:37–40.
- Kotchoubey B, Lang S, Herb E, Maurer P, Schmalohr D, Bostanov V, et al. Stimulus complexity enhances auditory discrimination in patients with extremely severe brain injuries. *Neurosci Lett* 2003;352:129–32.
- Kotchoubey B, Lang S, Mezger G, Schmalohr D, Schneck M, Semmler A, et al. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. *Clin Neurophysiol* 2005;116:2441–53.
- Laureys S, Faymonville ME, Degueldre C, Del Fiore G, Damas P, Lambermont B, et al. Auditory processing in the vegetative state. *Brain* 2000;123:1589–601.
- Luauté J, Fischer C, Adeleine P, Morlet D, Tell L, Boisson D. Late auditory and event-related potentials can be useful to predict good functional outcome after coma. *Arch Phys Med Rehabil* 2005;86:917–23.
- Morlet D, Bouchet P, Fischer C. Mismatch negativity and N100 monitoring: potential clinical value and methodological advances. *Audiol Neurotol* 2000;5:198–206.
- Multi-Society Task Force on Persistent Vegetative State. Medical aspects of the persistent vegetative state (first of two parts). *N Engl J Med* 1994a;330:1499–1508.
- Multi-Society Task Force on Persistent Vegetative State. Medical aspects of the persistent vegetative state (second of two parts). *N Engl J Med* 1994b; 330:1572–1579.
- Näätänen R, Gaillard AWK, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol* 1978;42:313–29.
- Näätänen R, Pakarinen S, Rinne T, Takegata R. The mismatch negativity (MMN): towards the optimal paradigm. *Clin Neurophysiol* 2004;115:140–4.
- Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN. Disability Rating Scale for severe head trauma: coma to community. *Arch Phys Med Rehabil* 1982;63:118–23.
- Schiff ND, Purpura KP. Towards a neurophysiological foundation for cognitive neuromodulation through deep brain stimulation. *Thalamus Relat Syst* 2002;2:55–69.
- Schiff ND, Ribary U, Rodriguez Moreno D, Beattie B, Kronberg E, Blasberg R, et al. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain* 2002;125:1210–34.
- Schröger E. Application of ERP measures in psychological research. Measurement and interpretation of the mismatch negativity. *Behav Res Methods Instrum Comput* 1998;30:131–45.
- Tremblay K, Kraus N, McGee T. The time course of auditory perceptual learning: neurophysiological changes during speech-sound training. *NeuroReport* 1998;9:3557–60.
- Wilson JTL, Pettigrew LEL, Teasdale G. Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998;15:573–85.
- Working Party of the Royal College of Physicians. The vegetative state: guidance on diagnosis and management. *Clin Med* 2003;3:249–254.