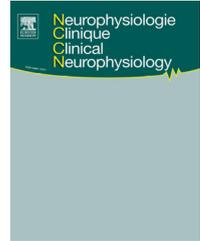


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Visual processing during recovery from vegetative state to consciousness: Comparing behavioral indices to brain responses



Traitement des informations visuelles en phase de récupération de l'état végétatif vers l'état conscient : étude comparée des indices comportementaux et des potentiels évoqués cérébraux

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Consciousness;
Visual evoked potentials

Summary

Background. – Auditory stimulation is often used to evoke responses in unresponsive patients who have suffered severe brain injury. In order to investigate visual responses, we examined visual evoked potentials (VEPs) and behavioral responses to visual stimuli in vegetative patients during recovery to consciousness.

Methods. – Behavioral responses to visual stimuli (visual localization, comprehension of written commands, and object manipulation) and flash VEPs were repeatedly examined in eleven vegetative patients every two weeks for an average period of 2.6 months, and patients' VEPs were compared to a healthy control group. Long-term outcome of the patients was assessed 2–3 years later.

Results. – Visual response scores increased during recovery to consciousness for all scales: visual localization, comprehension of written commands, and object manipulation. VEP amplitudes

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MOTS CLÉS

Traumatisme crânien ;
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État de conscience minimale ;
Conscience ;
Potentiels évoqués visuels

were smaller, and latencies were longer in the patient group relative to the controls. VEPs characteristics at first measurement were related to long-term outcome up to three years after injury.

Conclusions. – Our findings show the improvement of visual responding with recovery from the vegetative state to consciousness. Elementary visual processing is present, yet according to VEP responses, poorer in vegetative and minimally conscious state than in healthy controls, and remains poorer when patients recovered to consciousness. However, initial VEPs are related to long-term outcome.

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Résumé

Objectifs. – Des stimuli auditifs sont souvent appliqués aux patients non répondants qui souffrent de traumatisme crânien sévère. Nous avons étudié les processus visuels des patients en état végétatif au cours de leur évolution vers un état de conscience au moyen de potentiels évoqués visuels (PEV) et de réponses comportementales à une stimulation visuelle.

Méthodes. – Les réponses à la stimulation visuelle – localisation visuelle, compréhension des instructions écrites, et manipulation d'objets – et les PEV ont été mesurés toutes les deux semaines durant une période moyenne de 2,6 mois chez onze patients en état végétatif au cours de leur évolution vers un état de conscience. Les PEV des patients étaient comparés à ceux mesurés dans un groupe de sujets témoins. Une mesure de la récupération à long terme a été réalisée 2 à 3 ans plus tard.

Résultats. – Les réponses visuelles comportementales étaient plus grandes au cours de l'évolution de l'état végétatif vers l'état de conscience pour toutes les sous-échelles. Les amplitudes des PEV étaient moindres et les temps de latence étaient plus longs chez les patients par comparaison au groupe témoin. Les caractéristiques des PEV lors de la première mesure étaient corrélées au niveau de récupération à long terme.

Conclusion. – Nos résultats montrent une amélioration des réponses visuelles parallèlement à la récupération de la conscience chez les patients initialement en état végétatif. Le traitement visuel élémentaire est présent, mais, au vu des PEV, moindre chez les patients en état végétatif et en état de conscience minimale par comparaison aux sujets témoins et il demeure moindre chez les patients ayant récupéré un état de conscience plus élevé. Cependant, les PEV obtenus initialement sont corrélés avec la récupération à long terme.

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Introduction

It has been increasingly evident that clinical assessment of unresponsive, severely brain injured patients using behavioral observation methods alone can lead to misdiagnoses [10,51], as this merely quantifies the (absence of) behavioral reactions to the environmental input. Therefore, there is an increasing need for brain imaging or neurophysiological techniques aimed at detecting the level of consciousness in these patients [12,13,49]. Several studies have evidenced brain responses, which could be interpreted as signs of conscious awareness of the environment in patients who had been diagnosed as in a vegetative state (VS) [34], as they did not manifest any behavioural signs of consciousness [4,6,13,45,49,50]. Optimal methods to diagnose unresponsive patients are being investigated intensively, the next step being the development of cheaper, portable, widely available bedside techniques such as electroencephalography (EEG) [6,13], perhaps combined with transcranial magnetic stimulation (TMS) [49].

Among electrophysiological measurements, event-related potentials (ERPs) such as mismatch negativity (MMN) and P300 are regarded as markers of key stages

in the information processing hierarchy leading up to conscious perception. Recently, the use of ERPs in coma, vegetative and minimally conscious state (MCS) has been described extensively [9,14,52], both as a prognostic tool and as possible markers of consciousness.

As regards *prognosis*, the presence of a P300 has been found to be of some predictive value for neurological outcome at the early stages of coma. Thus, 80–100% of comatose patients, of traumatic and non-traumatic aetiologies, who exhibited a P300, regained consciousness [26,30,35]. However, no conclusions on prognosis can be drawn from the absence of P300, as patients without a P300 were found to have good or bad outcomes alike. In other words, using the presence of the P300 in the early stages of coma as a predictive tool for final outcome is a test with high sensitivity but low specificity. At a later stage after the injury, P300 was found to occur both in VS/unresponsive wakefulness syndrome (UWS) [30,32,37,38,40] and MCS [38,39] patients. Fischer et al. [21] found a relation between the occurrence of ERPs and the aetiology of VS/UWS or MCS, as P300 responses were mainly found when the patients' state was not due to anoxia. In an earlier trial, we found an almost perfect correlation between mismatch negativity

amplitudes and the recovery from VS/UWS to consciousness [54]. One case study describes the improvement of ERPs from the 6th month after injury; this patient emerged from VS/UWS after 20 months [17]. Studies also revealed that ERPs could sometimes be evoked in VS/UWS and MCS [32,38,54], especially when salient stimuli were used, such as patient's name [39,46], speech [37], and musical notes [37]. No large differences were found between VS/UWS and MCS.

Whether these ERPs are also *markers of consciousness* has been the topic of recent research in VS/UWS and MCS patients [5–7,18,19,50]. Bekinschtein et al. [5] and Faugeras et al. [18,19] used a derived function of the oddball paradigm, which they called the ERP Local-Global Paradigm. Only conscious individuals presented a global effect, which is more closely related to the P3b. In addition, by using extensive mathematical models on EEG data derived from the MMN paradigm, Boly et al. [6] observed that the only significant difference between patients in VS/UWS and controls was an impairment of backward connectivity from frontal to temporal cortices, indicating that top-down communication from frontal to parietal networks would be a prerequisite for consciousness.

In most studies, auditory stimulation is being used to evoke brain responses, whereas other sensory modalities could also provide helpful information about the inner world of unresponsive patients. Behavioural observation scales, e.g. the JFK Coma Recovery Scale-revised (CRS-R) [25] and the Western Neuro Sensory Stimulation Profile (WNSSP) [3], describe a multimodal stimulation approach to learn about functional (dis)abilities (e.g. arousal/attention; auditory functioning; visual functioning; motor functioning; verbal functioning). Each of these functions should be additionally tested by a set of neurophysiological methods, complementing behavioral observation. The determination of the capabilities and rehabilitation possibilities of a non-responsive patient will inevitably require 'tailor-made' procedures [55]. An excellent example of such a multimodal approach was described by Coleman et al. [11], who combined electrophysiological and functional brain imaging tools with behavioural scales.

We examined rudimentary visual perception using visual evoked potentials (VEPs) in a longitudinal design, and related these brain responses to the patients' visual functioning as measured by behavioural observation during their recovery to consciousness. VEPs are used primarily to measure the functional integrity of the visual pathways from retina to the visual cortex. Therefore, abnormalities of the retina, optic nerve, optic chiasm, optic radiations or visual cortex may result in abnormal VEPs. White-matter lesions anywhere along this pathway will slow down or even stop neural transmission, which will result in increased latencies of VEP components. VEPs are very well suited to quantify the functional integrity of the optic pathways. Other reasons to focus on visual information processing are, firstly, that the interpretation of perception in terms of visual orientation towards stimuli and visual tracking has been postulated for purely clinical reasons and has been regarded as a 'milestone' in recovery [24]. Secondly, visual perception is the most dominant sense in human conscious perception; it dominates all other senses when conflicts between

senses occur [33]. Thirdly, vision might play an important role in recovery from VS, because without intact vision, active manipulation of objects may be misguided or not initiated at all, since no definite goals of action are available [33].

VEPs are often used in the acute phase of coma, in combination with other evoked potentials (EPs) such as somatosensory and brainstem auditory EPs (SSEP and BAEPs), in order to assess the neurological condition of comatose patients. At this acute stage, EPs can be of large predictive value and many studies have demonstrated their usefulness in predicting mortality and outcome [1,20,29,41,47,53,57]. Thus, a poor outcome is likely to follow absent BAEPs and SSEPs in the acute phase after severe brain damage. In particular, SSEPs measured in the first week post-injury in anoxic brain damage appear to be most useful to predict a poor outcome [57]. In addition, when comatose patients were followed longitudinally, the changes in their overall condition were related to the presence, abnormality or absence of BAEPs, SSEPs, and VEPs [28,29,31,32]. Flash VEPs may be especially useful in the acute phase when SSEPs are less reliable, in which case VEPs can be used to provide further insight into prognosis for a individual patient [29,31,32].

All the above findings refer to the acute phase, that is, up to about four to six weeks after the injury. We addressed the issue of how recovery to consciousness occurs in the post-acute phase: what happens in the brain in the recovery period from VS to consciousness? We attempted to gain insight into the aspect, changes, and predictive value of VEPs. Research on both recovery processes and VEPs usefulness as a tool to assess visual processing is actually scarce in VS and MCS patients. Hildebrandt et al. were among the few to record VEPs in hypoxic VS patients and investigate their predictive value together with SPECT [33]. Patients who recovered always had a VEP, together with higher perfusion in the visual cortex and in the precuneus. There was a strong association between occipital and parietal perfusion and the presence of a VEP, underlying the importance of the occipital lobe for recovery. In a PET study, Menon et al. [42] visually presented photographs of familiar faces in a VS/UWS and a MCS patient who subsequently recovered to consciousness. Compared to the meaningless picture, the visual association areas encompassing the fusiform face area showed significant activation. No behavioural evidence of awareness of the environment was observed, except occasional visual tracking of family members. Using fMRI, Coleman et al. [11] described a VS/UWS patient who was able to perceive motion (V5/MT activation), objects (appropriate parahippocampal activation in response to pictures of houses), and faces (fusiform gyrus activation), although he did not exhibit any clinical evidence of being able to respond to commands.

To the best of our knowledge, this is the first study reporting VEPs to visual stimulation, in a longitudinal design during recovery from VS/UWS to consciousness. It was expected that changes in the amplitude and/or latency of VEPs would occur with recovery. VEPs in patients were expected to become increasingly similar to VEPs recorded in a control group. Additionally, we examined whether VEPs were of prognostic value for both recovery to consciousness and long-term outcome.

Materials and methods

Participants

Eleven patients from the Rehabilitation Centre Leijpark (Tilburg, The Netherlands) participated in this study. All patients involved in the Early Intensive Neurorehabilitation Programme (EINP) were children and young adults. They were in a VS/UWS or MCS as a result of severe brain damage acquired between November 2002 and January 2004 [15]. This treatment aims to maximize patient's ability to process and respond to stimuli and information of increasing variety and complexity. The rationale of the program is based on providing structured sensory input and preventing deprivation in order to trigger natural recovery processes [15]. Eilander et al. (2005) showed that patients who participated in this program had a more favorable outcome than predicted by 'The Multi-Society Task Force on Permanent Vegetative State' [43,44].

Eight patients were male. Age at the time of injury ranged from 6 to 25 years ($M=16.6$ years; $SD=5.3$). Time since injury at admission ranged from 1.9 to 6.6 months ($M=3.5$ months; $SD=1.5$). All but two patients suffered from traumatic brain injury caused by traffic accidents. All patients were in VS/UWS at the start of the program (see Table 1 for individual initial diagnosis). All patients participated in this study following informed consent given by one of the parents, a legal representative, or partner. The duration of the patients' participation in the program ranged from 1.5 to 4.3 months ($M=2.6$ months; $SD=0.8$). See Table 1 for a detailed description of the patients participating in this study.

A normal control group consisting of 22 persons (12 males, 55%), matched for mean age ($t(32)=0.67$, $P=0.51$), was investigated on a single occasion. All of the participants took part in this study following informed consent given by one of the parents or a legal representative (age < 16 years), or by themselves (age = 16). The study has been approved by METTOP (a certified Dutch Medical Ethics Committee for research with patients).

Observation scales

To assess the level of consciousness (LoC), a categorization was used based on the definitions described by the 'International Working Party Report on the Vegetative State' [2], and the Aspen Neurobehavioural Conference [23]. The categorization system describes a comatose state, three vegetative sub-states, three non-vegetative sub-states [7,24], and a conscious state (see Table 2 for detail).

This classification scale showed high reliability and validity [16]. The inter-rater reliability (Spearman's rho) varied between 0.85 and 0.94; Cohen's weighted Kappa varied between 0.90 and 0.95. The intra-rater reliability was 0.96 and the intra-rater agreement was 0.94. Correlation of the scores of the rated scores with the Western Neuro Sensory Stimulation Profile (WNSSP) [3] varied between 0.85 and 0.90, and with the Disability Rating Scale (DRS) [48] between 0.88 and 0.94 [16].

The rehabilitation physician determined overall LoC for each patient at the end of the programme (LoC_{discharge}), following discussion with the multidisciplinary treatment

team. Note that the level of consciousness at discharge was measured independently of the VEP measurements, often more than one week thereafter. Thus, the LoC_{discharge} did not necessarily correspond to a particular VEP measurement for a given patient.

Visual functioning was assessed using the WNSSP [3]. The WNSSP was specifically developed to assess the cognitive status and communicative performance in severely impaired head-injured patients. The WNSSP consists of 33 items that assess patient's arousal and attention, expressive communication, and response to auditory, visual, tactile, and olfactory stimulation. Six subscales (arousal and attention, auditory comprehension, visual comprehension, visual tracking, object manipulation, and expressive communication) and four additional observations (response to sound, speech, smell, and touch) have been delineated, which assess specific aspects of a patient's behavior and provide a means for evaluating a patient's pattern of response. The total score ranged from 0 to 113 (the higher the better). We used the following WNSSP items for assessment of visual functioning:

- localization (item 16–22): horizontal and vertical tracking (e.g. mirror, picture, object, individual);
- the total score ranges from 0 to 18 (the higher the better);
- comprehension of written commands (item 23–27): patient's ability to follow single stage written commands (shake my hand; open/close your mouth; stick out your tongue; open/close your eyes; raise your eyebrows; move 'body part'). The total score ranges from 0–25 (the higher the better);
- object manipulation (item 30–32): patient's ability to demonstrate conventional use of common objects (e.g. spoon, comb, pencil). The total score ranges from 0–15 (the higher the better).

Therefore, total score on visual functioning ranges from 0–58 (the higher the better).

To determine the long-term functional outcome, we used the DRS [48] as well as the Extended Glasgow Outcome Scale (GOSE) [56]. 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. [48]:

- 1 = dead (score 30);
- 2 = vegetative state (score 22-29);
- 3 = extremely severely disabled (score 17-21);
- 4 = severely disabled (score 12-16);
- 5 = moderately severely disabled (score 7-11);
- 6 = moderately disabled (score 4-6);
- 7 = mildly to partially disabled (score 1-3);
- 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 [56]. Outcome categories are:

- 1 = dead;
- 2 = vegetative state;

Table 1 Summary of patients' details.

Ptn	Gender	Age	Cause	GCS	T1	CT scan features ^a	LoC 1	LoC 2	DRS cat	GOSE	T2
1	M	17.6	Traffic accident	2t	72	Epidural haematoma (right), punctual haemorrhages, diffuse white matter lesions	3	4	3	3	3.0
2	M	20.8	Traffic accident	4	35	Skull fracture, intracerebral haemorrhages, atrophy, hypodensity, diffuse white matter lesions, punctual haemorrhages subcortical left and right, brain stem lesion	4	4	4	3	3.0
3	M	15.4	Traffic accident	4	33	Skull fractures, arachnoid haemorrhages, contusion and punctual haemorrhages (right frontal, temporal, parietal), diffuse swelling	2	5	4	3	2.9
4	M	25.2	Traffic accident	4	64	Skull fracture, oedema and punctual haemorrhages (cortical), diffuse swelling, and diffuse white matter lesions	2	8	6	3	2.7
5	M	8.4	Cerebral haemorrhages	2t	33	Intraventricular and intracerebral haemorrhages, left cortical	3	7	7	3	2.6
6	F	18.8	Traffic accident	2t	29	Oedema, ischemia, high intracranial pressure, diffuse swelling	4	8	4	3	2.4
7	M	17.5	Traffic accident	4	13	Oedema, intraventricular and intracerebral haemorrhages, focal lesions (subcortical, brainstem), diffuse white matter lesions	3	8	7	6	2.5
8	M	21.8	Traffic accident	5	26	Punctual haemorrhages, intraventricular haemorrhage (left), diffuse swelling, diffuse axonal injury	2	4	3	3	2.5
9	F	15.7	Traffic accident	4	30	Subarachnoid haemorrhage (right), high intracranial pressure, oedema (right subcortical and brainstem)	2	8	5	3	2.4
10	M	17.2	Traffic accident	3	12	Intraventricular haemorrhages (bilateral), multiple punctual haemorrhages, large haemorrhage in basal ganglia, and right frontal, oedema (mainly left periventricular white matter)	2	5	1	1	2.2
11	F	15.2	Pneumonia + sepsis	3	57	Hypodensity in basal ganglia and cortical temporoparietal, anoxia, cortical and cerebellar atrophy, diffuse white matter lesion	2	3			

Ptn: patient; F: female; M: male; age: age at injury in years; GCS: Glasgow Coma Scale at admission hospital; T1: time at ICU in days; LoC 1: level of consciousness first measurement; LoC 2: level of consciousness end of EINP; DRS: Disability Rating Scale; GOSE: Glasgow Outcome Scale extended; T2: time of outcome after injury in years.

^a Diagnoses based on the medical report in the acute phase.

Table 2 Levels of consciousness (LoC).*Coma*

Eyes are closed all the time. No sleep–wake cycles present

All major body functions such as breathing, temperature regulation or blood pressure can be disturbed. Generally, no reactions are noticed after stimulation. Sometimes, reflexes (stretching or flexing) are observed as a reaction to strong pain stimuli. No other reactions are present

Vegetative presentations

The patient shows sleep–wake cycles, but not a proper day–night rhythm. Most of the body functions are normal. No further ventilation is required for respiration.

Very little response (hyporesponsive): generally, no response after stimulation. Sometimes, delayed presentations of reflexes are observed

Reflexive state: the stimuli often result in massive stretching or startle reactions, without proper habituation. Sometimes these reactions evolve into massive flexing responses. Roving eye movements can be observed, without tracking. Sometimes grimacing occurs after stimulation

High active level and/or reactions in stimulated body parts: generally spontaneous undirected movements. Retraction of a limb following stimulation. Orientation towards a stimulus, without fixating. Following moving persons or objects, without fixating.

Minimally conscious state(s)

Patient remains awake most of the day

Transitional state: following and fixating of persons and objects. Generally more directed reactions to stimuli. Behavior 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

Inconsistent minimally conscious state: occasionally obeying simple commands. Total dependency. The patient has obvious cognitive disturbances and is unable to think comprehensively

Consistent minimally conscious state: the patient obeys simple commands. Many cognitive disturbances remain. Total dependency

Consciousness

The patient is alert and reacts spontaneously to his/her surroundings. Functional understandable mutual communication is possible, sometimes with technical support. Cognitive and behavioral disturbances can still be present

- 3 = lower severely disabled;
- 4 = upper severely disabled;
- 5 = lower moderately disabled;
- 6 = upper moderately disabled;
- 7 = lower good recovery;
- 8 = upper good recovery.

Recording and analyses of visual evoked potentials

The visual stimuli were 300 white flashlights (duration: 20 μ sec), which were presented with a frequency of 1 Hz. Flashlights were presented bilaterally using a 'White Flash Nihon Kohden model EEG-4314 F/G'. The lamp was at a distance of about 30 cm from the participant.

The EEG was recorded using actively shielded pin-electrodes (ActiveTwo System, BioSemi, The Netherlands; sampling rate 8 kHz; Common Mode Rejection Ratio > 120 dB). All equipment was approved for safety by a Metron QA-90 Safety tester in the Tweesteden Hospital (Tilburg, The Netherlands). The electrodes were placed using a head cap and electrode gel (Parker Signa) according to the 10/20 System, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz. Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from infraorbital and supraorbital regions of the two eyes in line with the pupil.

Data analyses were performed with BrainVision Analyser. EEG signals were band-pass filtered (3–100 Hz, 48 dB/octave). The raw data were segmented into 300 epochs, including a 100 ms pre-stimulus baseline, and a 500 ms post-stimulus response time. EOG artefacts were corrected according to a linear regression procedure [27]. Peak amplitudes and latencies were examined at the Oz electrode with reference to Fz. VEPs consist of alternating negative and positive waves: N1, P1, N2, P2, N3, P3, respectively. Long-latency peaks N2, P2, and N3 were assessed in terms of their presence, interpeak latencies, and peak-to-peak amplitudes (N2-P2 and P2-N3). Peak detection was performed semi-automatically. We searched for local maximum in each peak-interval: N1 (50–100 ms), P1 (80–120 ms), N2 (120–180 ms), P2 (120–180 ms), and N3 (200–300 ms). Automatic peak detection was followed by visual inspection, after which corrections were sometimes made when necessary.

Procedure

Nine days after a patient was admitted to the rehabilitation center, the first measurement took place. Patients were examined while they were lying in a bed in a quiet room with a constant temperature (23 ± 1 °C). All measurements were performed every two weeks at the same time of the day, between 10:30 a.m. and 11:30 a.m. Total VEP measurement

lasted 5 min. LoC was determined in the same week as the EP measurements by a rehabilitation physician, based on a discussion by the multidisciplinary treatment team. The WNSSP was administered every two weeks by the same neuropsychologist. These assessments were performed until the patient was discharged. Discharge followed when:

- a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities;
- or a patient did not show any recovery in a period of at least six weeks during the program.

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). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

The control group was measured once, in the same position and location, at different times of the day. They performed exactly the same tasks as the patients.

Statistical analysis

The longitudinal changes of visual functioning according to the WNSSP and VEP characteristics were analyzed as a function of LoC using a linear Mixed Model procedure (SPSS MIXED). This procedure is especially adequate to analyze changes in heterogeneous groups such as patients recovering from brain injury [22]. Mixed models use all available data, can properly account for correlation between repeated measurements on the same subject, and have greater flexibility to model time effects [36]. LoC was included as fixed factor and the individual subjects were included as random factors.

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 values of the VEPs for outcome were examined, using linear regression analyses.

Results

Behavioral indices of recovery

Level of consciousness (LoC-score)

At admission, the patients' average LoC score was reflexive vegetative ($M = 2.6$, $SD = 0.81$, range 2–4). The average LoC score increased to the inconsistent minimally conscious state ($M = 5.8$, $SD = 1.9$, range 3–8) at discharge. Five patients reached a conscious level (LoC 7 or 8), 2 patients were still in the MCS (LoC 5 or 6), and 4 patients were still in the VS/UWS (LoC 2-4) at the end of the program.

Overall, these data indicate that during the program the patient group improved on the mean level of consciousness (see Fig. 1). However, the LoC score at discharge was not related to the LoC score at the start of the programme. A regression analysis resulted in an equation of $LoC_{discharge} = 4.903 + 0.347 \times LoC_{initial}$ $R = 0.020$, $R^2 = 0.020$, Adjusted $R^2 = -0.089$, $F(1,9) = 0.183$, $P = 0.679$. Long-term outcome scores on the DRS and GOSE could be obtained for 10 patients. Two to three years after the injury the mean score on the DRS was 'severely disabled' ($M = 4.4$, $SD = 1.9$,

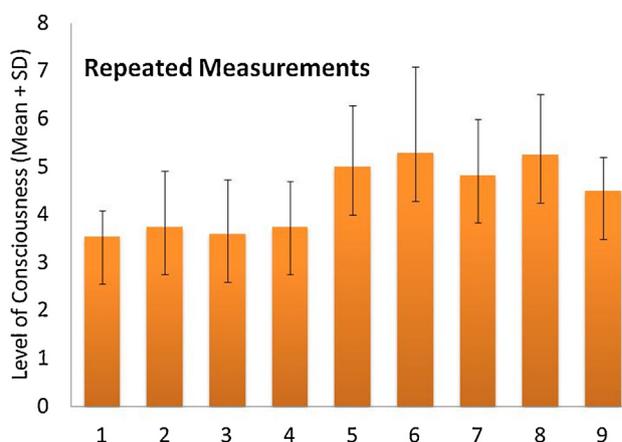


Figure 1 This figure shows the patients' level of consciousness (LoC), according to Table 2, during EINP participation. The average LoC score increased to the inconsistent minimally conscious state ($M = 5.8$, $SD = 1.9$, range 3–8) at discharge. Five patients reached a conscious level (LoC 7 or 8), 2 patients were still in the MCS (LoC 5 or 6), and 4 patients were still in the VS/UWS (LoC 2-4) at the end of the programme.

range 1–7), and the mean score on the GOSE was 'low level severely disabled' ($M = 3.1$, $SD = 1.2$, 1–6). See Table 1 for exact patient information.

With recovery to consciousness, scores on visual functioning improved according to the WNSSP assessment. Fig. 2 shows the progression in vision on localization (2a), comprehension of written commands (2b), object manipulation (2c), and total visual responses (2d). Visual functioning increased with recovery to consciousness in all dimensions: localization $F(6.19) = 3.47$, $P < 0.05$; comprehension of written commands $F(6.12) = 6.37$, $P < 0.01$; object manipulation $F(6.20) = 12.61$, $P < 0.001$; total visual response $F(6.20) = 8.61$, $P < 0.001$.

Repeated measurements of VEPs

The amplitudes and latencies of the different VEP components did not vary as a function of the level of consciousness (see Table 3 for means and standard deviations). No statistically significant effect of LoC, neither on VEP amplitudes nor on latencies was found. VEP components did not appear to change with recovery to consciousness ($F_s < 1$; $p_s > 0.50$). Fig. 3 shows an example for latencies and amplitudes in the patient group over LoCs. Fig. 4 presents an example of a VEP recorded in Patient 9 (Table 1).

In addition, VEP characteristics were not related to recovery of visual functioning. Amplitudes and latencies did not significantly change with increasing scores on the visual scales of the WNSSP ($F_s < 1.3$, $p_s < 0.30$). Fig. 5 shows an example for a patient's amplitudes and latencies for WNSSP scores on object manipulation:

Comparison of VEPs between patients and healthy controls

The data collapsed into each LoC were statistically tested against the healthy control group by means of t -tests. Overall, VEP latencies were longer and amplitudes were smaller in the patients relative to the controls, except for the N2 component. Because longitudinal trends were absent, each

Table 3 Visual evoked potentials amplitudes and latencies: means and standard deviations (in parentheses) for each level of consciousness and the norm group.

VEP characteristics	Level of consciousness							Norm
	2	3	4	5	6	7	8	
<i>Amplitudes</i>								
N2	-1.24 (2.22)	-3.15 (1.09)	-3.07 (0.86)	-2.79 (1.28)	-1.78 (1.99)	-1.28 (1.68)	-2.76 (3.14)	-2.38 (4.23)
P2	-0.48 (3.20)*	4.46 (1.60)**	5.67 (1.26)***	3.68 (1.88)***	3.67 (2.90)*	5.81 (2.44)*	8.59 (4.52)	12.84 (6.36)
N3	-2.77 (1.74)	-1.47 (0.84)**	-2.52 (0.65)**	-2.24 (0.96)**	0.80 (1.53)*	-1.60 (1.30)*	-3.27 (2.46)	-8.17 (6.81)
<i>Latencies</i>								
N2	144.35 (32.96)*	121.67 (16.96)***	125.63 (13.43)***	133.47 (20.20)***	108.09 (30.44)	134.37 (25.49)*	150.51 (46.62)	62.82 (15.36)
P2	138.92 (34.66)*	202.63 (17.68)***	190.64 (13.97)***	176.60 (20.99)***	145.28 (31.82)**	192.43 (26.69)**	184.57 (49.02)	109.24 (12.39)
N3	251.83 (34.40)*	261.34 (17.54)***	269.44 (13.85)***	261.37 (20.81)***	258.36 (31.57)**	263.67 (26.48)***	234.01 (48.65)	163.31 (19.32)
<i>Peak to peak</i>								
N2-P2	6.99 (3.40)	8.11 (1.75)**	9.20 (1.39)**	8.03 (2.08)**	9.83 (3.14)	8.99 (2.63)*	11.35 (4.81)	16.52 (7.75)
P2-N3	8.45 (3.73)	6.84 (1.95)***	8.67 (1.55)***	6.89 (2.34)***	6.04 (3.48)*	8.13 (2.91)*	11.86 (5.27)	21.31 (10.75)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for between group differences according to Mann-Whitney two independent samples tests (norm group against each level of consciousness in the patient group).

Table 4 Visual evoked potentials amplitudes and latencies: statistics Mann-Whitney test each level of consciousness against the norm group.

VEP characteristics	Level of consciousness (number of measurements)						
	2 (2)	3 (11)	4 (20)	5 (11)	6 (3)	7 (4)	8 (1)
<i>Amplitudes</i>							
N2	15 (0.47)	108 (0.61)	193 (0.50)	101 (0.45)	28 (0.68)	41 (0.83)	9 (0.76)
P2	2 (0.04)	33 (0.001)	77 (<0.001)	25 (<0.001)	9 (0.05)	11 (0.02)	6 (0.45)
N3	9 (0.18)	38 (0.002)	90 (0.001)	47 (0.005)	4 (0.02)	14 (0.03)	6 (0.45)
<i>Latencies</i>							
N2	0 (0.02)	19 (<0.001)	9 (<0.001)	0 (<0.001)	28 (0.72)	10 (0.02)	0 (0.10)
P2	3 (0.05)	11 (<0.001)	5 (<0.001)	10 (<0.001)	2 (0.01)	5 (0.006)	0 (0.10)
N3	0 (0.02)	4 (<0.001)	0 (<0.001)	5 (<0.001)	0 (0.006)	0 (<0.001)	0 (0.10)
<i>Peak to peak</i>							
N2-P2	4 (0.06)	42 (0.003)	97 (0.002)	40 (0.002)	17 (0.18)	15 (0.04)	6 (0.45)
P2-N3	5 (0.08)	26 (<0.001)	63 (<0.001)	27 (<0.001)	6 (0.02)	9 (0.01)	4 (0.29)

Table 5 Predictive value of visual evoked potential (VEP) amplitudes and latencies at the first measurement.

	Outcome Scale								
	Level of consciousness at discharge			Long-term outcome: Disability Rating Scale			Long-term outcome: Glasgow Outcome Scale - Extended		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Amplitudes</i>									
N2	-0.11	0.24	-0.15	0.32	0.22	0.46	0.18	0.14	0.41
P2	0.23	0.11	0.58	-0.08	0.12	0.23	0.06	0.08	0.28
N3	-0.34	0.15	-0.59*	-0.12	0.19	-0.22	-0.23	0.09	-0.65*
<i>Latencies</i>									
N2	-0.01	0.01	-0.38	-0.02	0.01	-0.67*	-0.02	0.01	-0.74*
P2	-0.01	0.01	-0.23	-0.03	0.01	-0.86**	-0.02	0.00	-0.80**
N3	-0.00	0.01	-0.14	-0.02	0.01	-0.64*	-0.01	0.00	-0.64*
<i>Peak to peak magnitudes</i>									
N2-P2	0.19	0.10	0.56	-0.13	0.10	0.40	0.01	0.07	0.06
P2-N3	0.16	0.07	0.63*	-0.10	0.08	-0.06	0.07	0.05	0.45

* $P < 0.05$; ** $P < 0.01$.

individual LoC is different from the normal controls as well. None of the VEP characteristics in LoC 8 differed from the norm group; however, only one measurement existed within this LoC. Taken together, these data indicate that there were marked differences in VEP amplitude and latencies between the patients and the controls. See Table 3 for means and standard deviations of each LoC of the patients, and the norm group. See Table 4 for the exact Mann-Whitney U-values and P-values. Fig. 6 presents the grand average VEP of the norm group.

Predictive value of visual evoked potentials

The results of the linear regression analyses for predicting outcome by means of initial VEP amplitudes and latencies are presented in Table 5. The table shows that the level of consciousness, at time of discharge from the program, could be successfully predicted by the amplitude of the N3 and the size of the P2-N3 complex at the first measurement. More

negative (greater) N3 amplitude and a greater P2/N3 complex predicted higher LoC scores at the end of treatment. VEP latencies did not predict LoC at discharge. However, initial VEP latencies were of significant prognostic value in predicting *long-term outcome* (DRS and GOSE), not LoC at the end of treatment.

Discussion

We tracked longitudinal changes in elementary visual processing in individual patients as they progressed from VS/UWS to consciousness, and we attempted to predict outcome based on various measures of visual processing. We examined VEPs, which can give insight into the functional integrity of the visual pathways from the retina to the primary visual cortex. Visual processing was also assessed by behavioural observation according to the Western Neuro Sensory Stimulation Profile (WNSSP). Three visual domains

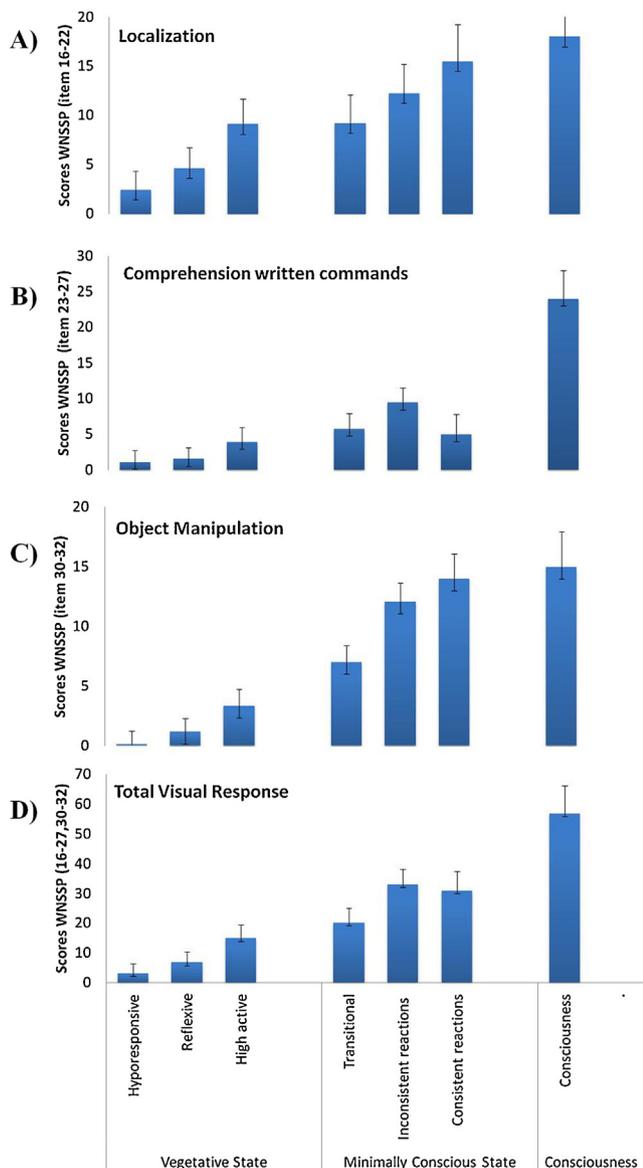


Figure 2 This figure shows the patients' scores on the WNSSP for each level of consciousness according to Table 2, during EINP participation. A. WNSSP score on 'localization'. B. WNSSP score on 'comprehension of written commands'. C. WNSSP score on 'object manipulation'. D. WNSSP score on 'total visual response'. Scores on the WNSSP increased with higher levels of consciousness, especially for 'localization' and 'object manipulation', and not that much for 'comprehension of written commands'.

were assessed: 'localization', 'comprehension of written commands', and 'object manipulation'. Patients' responses were compared to a healthy control group.

All patients involved in the early Intensive Neurorehabilitation Programme (EINP), were children and young adults in a VS/UWS or MCS as a result of severe acquired brain damage [15]. At the end of the program, five patients reached a conscious level (LoC 7 or 8), two patients were still in MCS (LoC 5 or 6), and four patients were still in VS/UWS (LoC 2-4). Overall, these data indicate that during the program

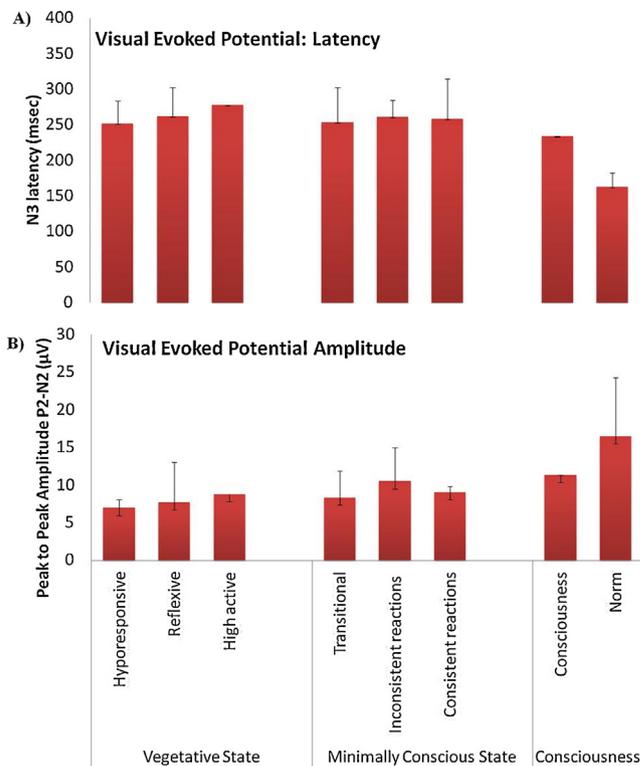


Figure 3 Here, some examples are presented of visual evoked potential (VEP) responses as a function of level of consciousness according to Table 2. A. Mean (SD) latency of N3 in milliseconds. B. Mean (SD) peak-to-peak amplitude P2-N2 in microvoltages. The conscious patients resembled the norm group the most, however also did significantly differ from them both for latency and amplitude.

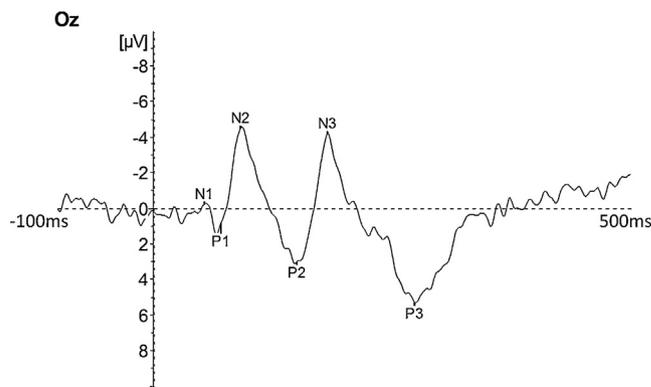


Figure 4 This figure shows an example of a visual evoked potential recorded at Oz during measurement 8 in patient 9.

the patient group improved as regards the mean level of consciousness.

Longitudinal study of VEPs

Clinical responses to visual stimulation according to the WNSSP improved during recovery to consciousness. Patients who recovered showed near-normative scores at the end of the program in all visual domains. However, our study unequivocally demonstrated the absence of any parallelism

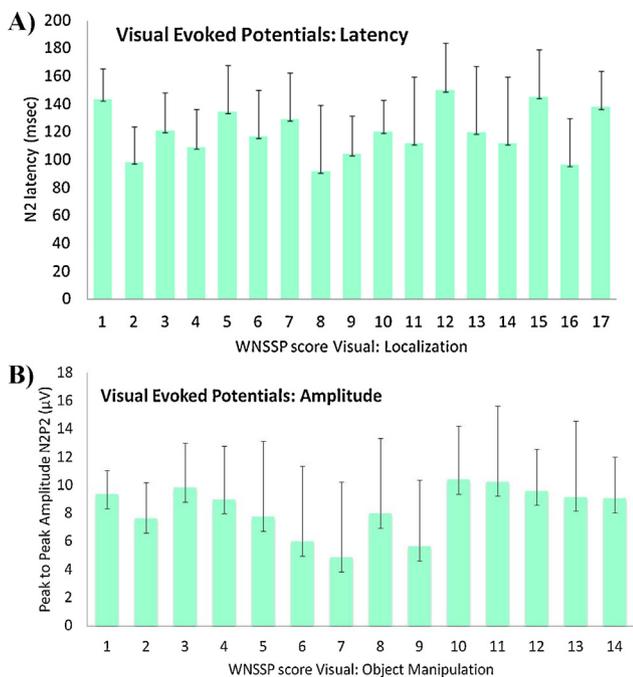


Figure 5 Here, some examples are presented of visual evoked potential (VEP) responses as a function of scores on visual processing according to the WNSSP. A. Mean (SD) latency of N2 in milliseconds related to WNSSP score on 'localization'. B. Mean (SD) peak-to-peak amplitude N2-P2 in microvoltages related to WNSSP score on 'object manipulation'. No general pattern can be recognized in either measure.

between the increase in the level of consciousness and improvement in scores on visual processing on the one hand, and changes in VEP latencies or amplitudes on the other. Such absence of longitudinal changes could be interpreted as an indication that the elementary sensory processing in this patient group was fully functional. However, the fact that VEPs amplitudes were consistently smaller and latencies consistently longer in the patients relative to controls suggests that elementary visual processing was actually poorer in patients versus controls. Another, more likely, hypothesis could be that these visual pathways that are assessed by flash VEPs are not the same as those that

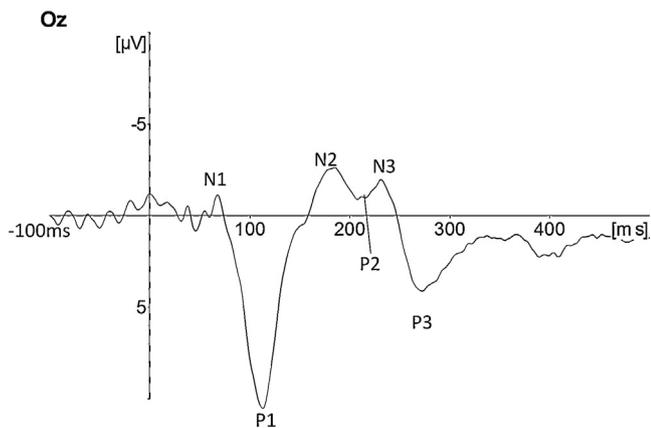


Figure 6 This figure shows the grand average of visual evoked potentials in the Norm Group recorded at Oz.

are involved in these aspects of visual processing that were clinically evaluated. In keeping with this hypothesis, Bruno et al. [8] investigated brain responses related to visual fixation in a vegetative state, and did not demonstrate any difference in the brain areas related to consciousness in patients with or without fixation capabilities.

Thus, flash VEPs and visual fixation might be brain responses too elementary to investigate recovery from VS to consciousness. When taking into account the progress these patients made on 'comprehension of written commands' and 'object manipulation' (Fig. 2) during recovery to consciousness, more cognitive paradigms of visual event related potentials might evoke brain responses resembling more the brain processing involved in (recovery to) consciousness. These WNSSP domains could be inspiring for future ERP research, since largest differences between levels of consciousness were found here also resembling the criteria of emergence from MCS to consciousness [24].

Prognosis

We also attempted to predict final outcome on the basis of early measurements. The level of consciousness at the end of the treatment programme could not be predicted based on the first clinical assessment of consciousness. Because VEPs have been shown to be of predictive value in the acute phase after the injury, we hypothesized that EPs would also be able to predict outcome in the post-acute phase. It turned out that initial VEP latencies, especially P2 latency, were able to predict long-term outcome, as determined by the DRS and GOSE two years after the end of the treatment. VEP amplitudes, especially for the N3 component (N3 amplitude versus baseline and P2-N3 amplitude), were related to the level of consciousness at the end of treatment and long-term outcome assessed with the GOSE.

To the best of our knowledge, this is one of the first studies in which VEPs were found to be of predictive value in the post-acute phase in VS/UWS. Only Hildebrandt et al. [33] already showed the presence of a VEP in hypoxic VS patients to be of predictive value. Guérit et al. [29,31,32] suggested that VEPs could be especially useful when SSEPs are unreliable, in which case VEPs can be used to give further insight into individual prognosis. Their results were obtained in the acute phase of coma whereas our results suggest that VEPs could be useful in the post-acute phase as well.

Limitations

Our study has two limitations. Firstly, our results are only preliminary; we describe a very small sample of young patients (aged between 8–25), suffering mostly from traumatic brain damage. Therefore, our results may not be readily extrapolated to older patients suffering from comas of different origins. Secondly, the final outcome of the patients participating in this study was somewhat restricted. Most patients did not regain full consciousness and severe disabilities persisted after the treatment period as well as in the long run. It is possible that the outcome in this patient group showed too little variability to allow more precise predictions.

Nevertheless, these findings certainly warrant further investigation of this important problem. Moreover, assessing visual responses during recovery from VS/UWS appears to be informative. Elementary visual processing might be critical in distinguishing patients who do and do not recover to consciousness. Hildebrandt et al. [33] also showed that higher perfusion in the visual cortex and in the precuneus by using SPECT measurement in patients who finally recovered from VS/UWS.

To summarize, we presented the first study of visual evoked potentials in VS/UWS patients in the post-acute phase during recovery to consciousness. VEPs did not change as a function of the increasing level of consciousness in individual patients. However, initial VEP P2 latency and VEP N3 component amplitude were particularly related to long-term outcome of these patients. In addition, elementary visual processing appears to be slower in patients when compared to healthy participants, irrespective of the level of consciousness.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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