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Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state☆

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See Editorial, pages 2253–2254

Abstract

Objective: To study the presence of electrophysiological indicators of remaining cortical functions in patients with persistent vegetative state (PVS) and minimally conscious state (MCS). Previous electrophysiological and PET data indicated that some PVS patients have partially intact cortical processing functions. However, it remains unclear whether the reported patients were representative for PVS population or just some exceptional cases.

Methods: Event-related brain responses to stimuli of different complexity levels, recorded in 98 patients with extremely severe diffuse brain injuries, 50 of which in PVS. Four main indicators of cortical functions were: (i) N1–P2 complex as an index of simple, undifferentiated cortical processing; (ii) mismatch negativity as an index of pre-attentive, probably unconscious, cortical orientation; (iii) P3 wave as an index of deep cortical analysis of physical stimuli, and (iv) brain responses to semantic stimuli.

Results: Cortical responses were found in all PVS patients with a background EEG activity >4 Hz. All responses investigated, including those to semantic stimuli that indicated comprehension of meaning, occurred significantly above chance, though less frequently than in patients with severe brain injuries who were conscious.

Conclusions: Cortical responses were lacking in most patients with severe EEG slowing (<4 Hz). Follow-up data revealed that the presence of a mismatch negativity, a short disease duration, and the traumatic etiology were related to a better outcome.

Significance: The data show that in a subpopulation of PVS patients with preserved thalamocortical feedback connections, remaining cortical information processing is a consistent finding and may even involve semantic levels of processing.

Keywords: Consciousness; Event-related potentials; Minimally conscious state; P300; Vegetative state

Vegetative state (VS: Jennett, 2002) (also known as apallic syndrome: Gerstenbrand, 1987) is the most severe chronic neurological syndrome characterized by the complete loss of all mental functions with remaining (sometimes enhanced) subcortical responses to stimulation. VS can be caused by head injury, brain anoxia, hemorrhage (particularly subarachnoidal hemorrhage), less frequently by

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encephalitis or toxic brain lesion, and usually follows a period of coma. In contrast to coma, brain stem functions are mostly intact, and sleep-wakefulness pattern can be nearly normal or slightly irregular (Andrews, 1997; Celesia, 1997; Giacino, 1997). The VS is regarded as 'persitent' (PVS) after the duration of one to 3 months, depending on the etiology (Bernat, 1992; Jennett, 2002; Kennard and Illingworth, 1995). Since most VS patients described in the present study were ill for more than one month, we shall use the terms 'VS' and 'PVS' synonymously.

The incidence of traumatic VS is estimated between 1 and 10 per 100,000 (Grossman and Hagel, 1996), and non-traumatic VS is as least as frequent. The prevalence of this condition lies between 56 and 140 per million (American Congress for Rehabilitation Medicine, 1995) (Multi-Society Task Force on the Persistent Vegetative State, 1994).

The diagnosis PVS is based entirely on the negative evidence, i.e. the lack of responses (Wade and Johnston, 1999). In contrast to coma, however, the definition of VS implies not simply absent responses but, rather, the lack of *purposeful* or *voluntary responses*, which makes the diagnostics particularly difficult leading to a high rate of diagnostic errors (Andrews et al., 1996; Childs et al., 1993).

In some severely brain-damaged patients, very weak and inconsistent 'purposeful or voluntary' responses can be observed. This borderline condition is referred to as 'minimally conscious state' (MCS) (American Congress for Rehabilitation Medicine, 1995; Cossa et al., 1999; Giacino and Kalman, 1997; Giacino et al., 2002). Clinical differentiation between VS and MCS is very difficult and based on the very subtle distinction between reflexive reactions in VS and sporadic, weak and inconsistent intentional actions in MCS (Giacino et al., 2002; Pilon and Sullivan, 1996; Shewmon et al., 1999; Strauss et al., 2000; Whyte et al., 1999).

These difficulties indicate that, in addition to clinical examination, instrumental techniques can be useful to obtain information not dependent on the patient's ability for overt responses. Thus, positron emission tomography (PET) data demonstrate a very low metabolic rate in the brain of PVS patients in rest, comparable with that in coma or in deep anesthesia (Rudolf et al., 1999; Tommasino et al., 1995). However, in some patients PET revealed fragments of well functioning cortex (de Jong et al., 1997; Owen et al., 2002), in which patterns of regional blood flow varied consistently as a function of stimulus features (Laureys et al., 2000a; Menon et al., 1998). Recent studies (Schiff et al., 1999, 2000) used combined recordings of PET and magnetoencephalography together with structural MRI and obtained some correlations between neurophysiological and behavioral indices of preserved cortical functions in 5 PVS patients (see also Laureys et al., 2000b).

Yet earlier, event-related brain potential (ERP) studies in PVS found occasional indices of cortical processing (Marosi et al., 1993; Rappaport et al., 1991; Reuter et al., 1989). These data were later replicated and extended in studies using more complex stimulation and larger groups of patients with extremely severe brain damage some of which were in PVS (Jones et al., 2000; Witzke and Schönle, 1996). In single cases, positive ERP findings were related to a successful outcome (Connolly et al., 1999).

As well known, the spatial resolution of ERPs is rather low. On the other hand, ERPs measure the neural activity as such in real time, not a secondary correlate of this activity (Marchand et al., 2002). ERP recording can be realized at patient's bedside, even at home. The other disadvantage of the ERP technique is that only cortical processes can be measured. In the case of PVS, however, this aspect is even advantageous because the presence of subcortical responses is without question, and the issue of interest is whether and to what extent cortical information processing takes place (Kotchoubey et al., 2002).

While the initial descriptions of PVS or 'apallic syndrome' (Jennett and Plum, 1972; Kretschmer, 1940) assumed at least functional decortication of such patients, PET and ERP data converge that some level of cortical processing can remain running in occasional PVS patients. However, it remains unclear whether the reported patients with remaining cortical processing are representative for the population of PVS patients or are just a few exceptional cases. A further problem specific for ERP studies is the subjectivity of visual assessment for presence versus absence of ERP components. These subjective evaluations are characterized by high fallibility and intra-judge variability even in experienced judges (Valdes-Sosa et al., 1987).

The present study should answer the question, how frequently cortical ERP responses can be found in PVS and MCS patients. These frequencies should be estimated as a function of complexity level of cortical processing (rather than at only one selected functional level, as in the previous ERP studies), and based upon replicable quantitative evaluation techniques rather than subjective expert judgments. The issue of processing levels was concerned in a recent study with a group of 15 PVS patients (Boly et al., 2004) most of whom displayed cortical activity in primary auditory areas (41 and 42 of Brodman) but, in contrast to both MCS and healthy control, no PVS patient showed activity in secondary areas such as the area 22.

Thus we expected that (i) middle-latency ERP components related to low-level cortical processing (mainly in primary sensory areas) would be present in all MCS patients and in some PVS patients, (ii) long-latency components related to higher levels of processing complexity (in secondary sensory and association areas) would be found in some MCS patients but not in PVS patients, (iii) all ERP components would be more frequent in patients with severe brain damage who are not in PVS or MCS any longer.

Furthermore, we intended not only to test several hierarchical levels of information processing in severely brain damaged patients, but also to check how strong is the presumed hierarchy. Specifically, two 'hierarchic complexity hypotheses' were formulated: (1) the processing of physically simple stimuli is necessary for the processing of more complex stimulus qualities; (b) the middle-latency ERP components such as N1 and the mismatch negativity, which are related to the activity of the sensory cortex and are supposed to manifest relatively simple processing mechanisms, are necessary for later components reflecting the activity of associative cortical areas and thus related to more complex processes (see, e.g. Howard, 2001; Kotchoubey, 2002; Näätänen, 1992; Näätänen and Winkler, 1999). If these hypotheses are correct, only simple processing functions should be examined in each severely damaged patient and, whenever no evidence for their presence has been found, the examination can be terminated because in no case a more complex function can be found in this patient. If these hypotheses are wrong, however, all functions should be examined in all patients.

1. Methods

1.1. Patients

A total of 105 patients with very severe and diffuse brain damage were examined. All of them were older than 15 and had intact or only slightly delayed auditory brain stem evoked potentials. The disability level according to Disability Rating Scale (Rappaport et al., 1982) varied between 6 (moderate) and 29 (extreme VS). No psychotropic drugs were administered at least for one week before examination. The study was approved by the Ethical Committee of the University of Tübingen Medical School. Informed consent was obtained from the patients' legal representatives. ERP examinations were terminated whenever a patient demonstrated even minimal symptoms of defense or aggression. The data of 7 patients were missed for this reason. The remaining 98 patients were subdivided into 4 groups:

Main group 1 (MG1, $N=38$): patients without any behavioral evidence of perception, communication, or purposeful motor actions, with dominant theta (4–7 Hz) or slow alpha (7.5–8 Hz) EEG activity, not suppressed by light. This EEG criterion was introduced for comparison with the MG2 described below. The diagnosis was PVS.

Main group 2 (MG2, $N=38$): patients with weak and inconsistent responses such as pursuit gaze movements. The dominant background EEG activity was between 4 and 8 Hz, which was non-responsive in 29 patients and weakly responded to stimuli in the remaining 9. The diagnosis was MCS in 34 patients. In 4 patients the diagnosis remained unclear (PVS or MCS) at the time of examination, but changed to MCS during the following several days. Since those 4 did not differ from the other patients in any respect, they were analyzed together.

The two main patient groups were comparable, the only factor differing between the two being the clinical diagnosis. However, this comparability was attained due to the selection of only those PVS patients without severe disturbances in the EEG. The importance of this factor was controlled in the Control group 1. In addition, patients with disorders of consciousness should be compared with individuals with intact consciousness. The numerous differences between severely impaired patients and healthy subjects make, however, a healthy control group meaningless. Therefore, a group of patients with severe brain lesions but able to consistent communication (Control group 2) was chosen for comparison with the second main group (i.e. MCS).

The Control group 1 (CG1, $N=12$) included patients clinically and neuropsychologically identical to those in the MG1, but characterized by a more pathological rest EEG: large diffuse delta-waves (1.5–3 Hz; 8 patients), flat EEG (3 patients), or alternation of delta activity and paroxysmal discharges (1 patient). The Control group 2 (CG2, $N=10$) consisted of severely brain-damaged but conscious patients, 7 of whom survived coma or a transient VS. The EEG was characterized either by fast theta (6–7 Hz) or slow alpha (8–9 Hz) oscillations which were suppressed by light.

In order to check the EEG classification made by means of visual inspection of clinical EEG traces, we additionally performed a Fourie analysis of 2.2 min rest EEG segments recorded at the beginning of our ERP examinations. In all patients in the two main groups a hump located in the theta band or (rarely) alpha band was observed (Fig. 1). No such hump was found in any patient of the CG1.

Detailed characteristics of the 4 groups are presented in Table 1. In 48 patients we obtained follow-up data 6 months after our examination. The remaining patients had to be discharged from the hospitals and the follow-up information was not available. The two subgroups (i.e. the 'preserved' and 'dropped out') did not differ in terms of the clinical diagnosis, age, gender, or electrophysiological variables.

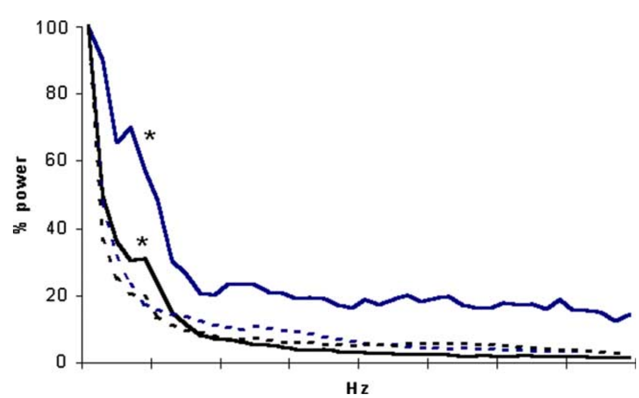

Fig. 1. Typical examples of the EEG frequency spectrum in 4 PVS patients two of which belonged to the Control group 1 (CG1, dashed lines), and two to the Main group 1 (MG1, solid lines). Pz lead. The spectral analysis is based on a 131.07 s time epoch (32758 points) of rest EEG. Hanning window was used. Each data point stands for a frequency range of 1 Hz, each tick on the *X*-axis, for 5 Hz. Asterisks indicate a relative increase of the power in the theta band in MG1 patients. This increase was lacking in all CG1 patients.

Table 1
Description of patient sample

	CG1	MG1	MG2	CG2	Total
Etiology					
Trauma	2	17[b]	12	5	36[b]
Anoxia	5	10	12		27
Hemorrhages[a]	4(4)	10(9)	13(13)	5(3)	32(29)
Fat emboli	1		1		2
Encephalitis		1			1
Male/female ratio	8/4	27/11	28/10	8/2	71 / 27
Age, years[c]	50 (20–76)	40 (18–69)	46 (15–75)	43 (15–61)	44 (15–76)
Time since accident, months[c]	7.9 (2–36)	6 (1.2–57)	13 (1.2–127)	4.3 (2–8)	8.7 (1.2–127)
Disability level[d]	26.3; 26 (25–28)	25.4; 25 (22–29)	19.9; 20 (17–24)	7.4; 7 (6–11)	18.3; 23 (6–29)
Follow-up data available	5	18	20	5	48
Improved	None	9	10	4	23

[a] Numbers in parentheses indicate patients with subarachnoidal haemorrhages, most of them as a result of an aneurysm rupture.
[b] Two of these patients had combined *traumatic and anoxic* brain lesions, with the contribution of the two causal factors being impossible to separate. These two patients were excluded from the analyses based on the etiological classification.
[c] Means, range in parentheses.
[d] According to DRS (Rappaport et al., 1982), with 0, no disability; 29, extreme VS, means; medians, range in parentheses.

However, there was one significant difference: follow-up data of non-traumatic patients were available more frequently than follow-up data of traumatic patients: $\chi^2(1)=5.47$, $P<0.05$. Clinical improvement was defined as follows: (a) for PVS patients, the diagnosis MCS or better; (b) for MCS patients, any diagnosis better than MCS, including a distinct communication ability, (c) for patients already communicating during the examination, an improvement of cognitive functions observed by at least two independent neuropsychologists. Patients who died after reaching these improvement criteria were regarded as 'improved' if the cause of death was unrelated to brain pathology (e.g. pneumonia). The improvement criteria were fulfilled by 23 of 48 patients.

1.2. Procedure

Three oddball paradigms were used in which two stimuli with unequal probabilities (0.85 and 0.15) were presented, the rare stimulus being referred to as 'deviant' or 'oddball'. In *Oddball I* simple sine tones were presented (1200 Hz—frequent standard, 700 Hz—deviant). Tone duration was 100 ms and onset-to-onset interstimulus intervals (ISI) were 900 ms. In *Oddball II* two 3-component harmonic chords were used instead of the sine tones. Finally, in *Oddball III* two natural sounds were presented: /o/ as a frequent stimulus, and /i/ as the rare deviant. Details of these experiments are described elsewhere (Kotchoubey et al., 2001).

MMN I was a mismatch negativity paradigm (Näätänen, 2000) with 700 sine tones (duration = 30 ms; ISI, 400 ms) 10% of which were deviants (247 versus 440 Hz in standards). *MMN II* was identical to MMN I, but with musical chords like in Oddball II. For details of the MMN experiments see Kotchoubey et al. (2003).

The oddball and MMN paradigms were designed to test 3 levels of cortical processes: primary undifferentiated auditory cortical responses expressed in components P1 (latency range 60–100 ms), N1 (90–140 ms), and P2 (150–220 ms); the MMN (latency range 150–300 ms) as a sign of primary (outside the focus of attention) auditory differentiation; and the P3 (300–500 ms) as a target response indicating a deeper level of differentiation. In principle, both MMN and P3 to deviant stimuli could be recorded in one single experiment. However, because recording the MMN requires more stimuli (at least several hundreds whereas the P3, at least in healthy subjects, can be clearly seen after 30–40 stimuli), and recording the P3 requires a longer ISI (at least 800–900 ms), such single experiment would require much more time than one MMN experiment and one oddball together.

Three paradigms were used to record cortical responses to semantic stimulus features (i.e. meaning). In the *Semantic oddball* word categories (animals, plants, jobs, body parts, and household objects) were used instead of single stimuli (Kotchoubey and Lang, 2001). The patients were instructed to count animal names and to ignore all other words. In the *Word pairs* task 100 pairs of one-syllable words spoken by a female voice were presented. Fifty pairs contained semantically closely related words (e.g. table-chair), and the remaining pairs contained unrelated words (Bentin et al., 1993; Hagoort et al., 1996). Finally, in the *Sentences* task (Connolly et al., 1992; Kutas and Hillyard, 1980) one hundred 7-word sentences were used. In 50 sentences, the last word was highly expected in the context, in the remaining 50 sentences, the last word was semantically incongruent. The same 50 final words were used, once as a congruent ending of a sentence, and once as a semantically incongruent ending of another sentence.

The experiments were presented in counterbalanced order. Each experiment entails two conditions (e.g. frequent versus rare, or related versus unrelated stimuli), which were presented in a pseudorandomized order with the following exceptions: in the MMN experiment no two deviants were allowed to appear in direct succession; in oddballs no more than 3 deviants were presented in a row, and in Word Pairs and Sentences, this rule was applied to each stimulus category.

The intensity of all tonal stimuli was 75 dB above the average threshold. The intensity of vowels and words was kept around this level.

1.3. EEG recording

The EEG was recorded by means of sintered Ag/AgCl electrodes according to the international 10–20 electrode system at F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 recording sites, referred to two mastoid electrodes which were linked via a 15 kOhm shunt. For the first time (according to the information obtained from NeuroScan, Inc.) we used Neuroscan as a portable system on a notebook computer for EEG recording at the patient's bedside. The vertical and horizontal electrooculogram (vEOG and hEOG) was recorded using two pairs of electrodes attached at the outer canthi of the two eyes (hEOG), as well as below and above one eye (vEOG). The signals were digitized at 250 Hz and filtered with a low-pass filter of 70 Hz and a high-pass filter of 0.3 Hz (24 dB/octave). An additional notch filter removed all frequencies between 45 and 55 Hz from the signal. After averaging, a further digital low-pass filter at 20 Hz was applied.

1.4. Data reduction and analysis

The EEG and EOG were chunked into epochs lasting for 400 ms including 20 ms pre-stimulus baseline (MMN I and II), 850 ms including 100 ms baseline (Oddball I, II and III), or 1100 ms including 100 ms baseline (the semantic paradigms). A regression procedure for correction of ocular artifacts (Gratton et al., 1983) covered these epochs. Then, all trials containing EEG amplitudes $>120\ \mu V$ were discarded. An experiment was considered valid if its each condition (e.g., standards and deviants) entailed at least 35 valid trials. These trials were averaged to obtain an ERP.

The analysis of the ERP waveforms began with a visual inspection by two experts, in order to assess the presence of the ERP component, like in Jones et al. (2000). On the next step, mean ERP amplitudes were measured in each single trial within a time window appropriate for that component. These data entered an analysis of variance with repeated-measures factors Topography I (frontal, central, parietal), Topography II (left, midline, right), and a factor Condition which contained 2 levels (standards versus deviants, or related versus unrelated words) and served as a between-trial factor. The ANOVA was conducted for each patient and experiment.

Generally, there are 5 criteria of an ERP component: its polarity, latency, duration, morphology, and topography. However, the validity of these criteria for evaluation of severe neurological patients should be critically examined. The 'typical' morphology of ERP waves described in the literature is the result of averaging across a group of subjects, so this criterion is not applicable when judging the presence of a wave in an individual. The topography is a more important criterion, but in patients with massive cortical lesions abnormal topography is not surprising. Furthermore, even mild brain injuries often lead to a latency delay of ERP components (Granovsky et al., 1998; Münte and Heinze, 1994). Therefore, in the present study we relied upon the polarity and the temporal features (latency and duration) only, with the latency criterion being one-edged: e.g. a slow positivity peaking earlier than a typical P3 cannot be a P3, but a positivity peaking later may be one. Thus we considered an ERP component as present when (i) the factor Condition or any of its interactions was significant, (ii) this effect was significant in a time window appropriate for the hypothesized wave (i.e. latency and duration criteria), and (iii) the polarity of the between-condition difference corresponded to the expected ERP component (i.e. polarity criterion). Greenhouse-Geisser non-sphericity correction was used when appropriate. The .05 significance level was one-tailed because, according to the polarity criterion, one-sided hypotheses were tested.

When a component was sought in several paradigms (for instance, we asked whether a patient showed at least one P3 in any task), the α-level was Bonferroni adjusted.[1] Finally, the components N1 and P2, which do not differentiate between conditions, counted when their overall difference from zero (and not the effect of Condition) was significant.

2. Results

2.1. General findings

The frequencies of occurrence of various ERP effects are presented in Table 2. With a nominal error probability of .05, we assumed that 5% findings could be significant per chance. Of course, this would be correct if each individual $P=0.05$, while in fact, Ps were *lower than* 0.05, some of them even lower than 0.001. Therefore, we overestimated the supposed 'chance positive rate' and, accordingly, underestimated the difference of our data from chance. Notwithstanding this underestimation, Table 2 shows that

[1] We also tried more conservative or more liberal α-levels, which resulted in a general decrease or increase of positive findings, respectively. Further, in oddball paradigms we attempted a wavelet transformation technique, also resulting in a slightly higher percentage of positive P3 findings. Importantly, however, all the tendencies and between-group differences remained the same regardless of the technique of individual analysis. To save space, the results obtained by varying statistical methods will not be reported.

Table 2
Presence of ERP components in patients with severe brain damage (in %)

Brain response	Groups			
	CG1	EG1	EG2	CG2
N1–(P2)	33*(36*)	89***(92***)	95***(97***)	100***
MMN	8(9)	65***(63***)	34***(38***)	100***
P3 (sine tones)	0	15(14)	8(4)	60***
P3 (complex tones)	0	22*(19)	31***(30***)	56***
P3 (vowels)	0	19(16)	22*(20)	56***
at least one P3 response	0	32***(30**)	36***(35***)	80***
P600 (semantic oddball)	0	23**(22*)	13(11)	44***
N400 (word-pairs)	0	14(16)	20*(18)	22
N400 (sentences)	0	23*(22*)	18(16)	14
At least one semantic response	0	22**(24**)	25**(24**)	60***

Numbers in parentheses indicate component frequencies when patients with less typical etiology (fat emboli, encephalitis) were excluded. Asterisks show how significantly the corresponding numbers differ from those expected by chance: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

the frequencies of occurrence substantially exceeded chance for most ERP components in all groups except the CG1.

Examples of patients' brain responses are presented in Fig. 2. Across all patients, more frequent N1 and P3 components were associated with the lower level of disability (DRS), traumatic etiology, and disease duration <6 months. However, these differences disappeared when the analysis was performed within each group. Traumatic patients were younger than patients with brain anoxia and hemorrhage (mean = 34.8 versus 48.4 years, $t=3.75$, $P<0.001$).

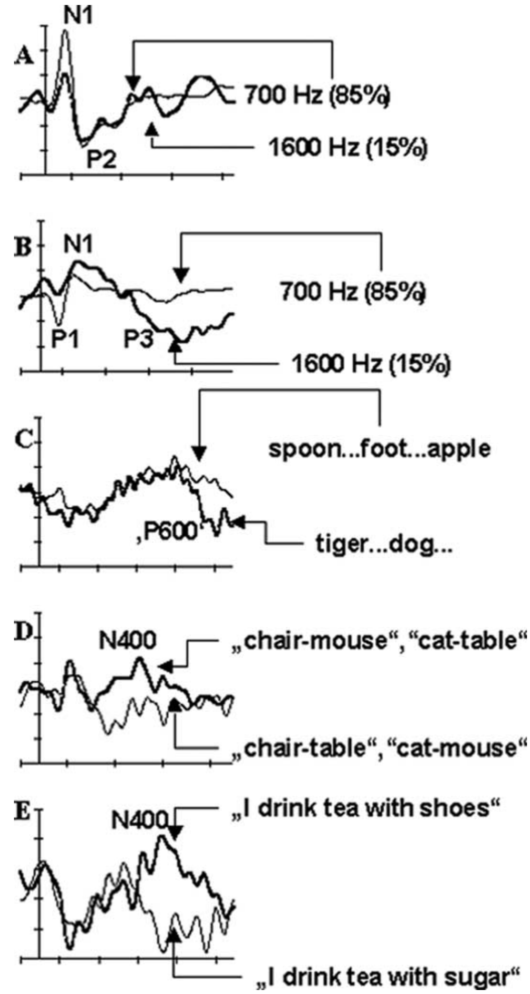

Fig. 2. Examples of various ERP phenomena in patients with severe brain damage. (A): Primary cortical components N1–P2—however, without any differentiation between frequent and rare stimuli, in a male patient, 51, anoxic brain injury. (B): Apart of the primary complex, a delayed P3 to rare stimuli in a female, 29, subarachnoidal hemorrhage. (C): A long-latency, significant ($P=0.014$) positive deflection ('P600') to the counted word category (animals) in the semantic oddball, a female, 19, PVS after a post-operative intraventricular hemorrhage. (D): An N400 in the Word pair experiment to semantically unrelated words, in contrast to a positivity to related words, in a male, 42, head injury. (E): An N400 to incongruent end words in the Sentence experiment, in a male, 61, MCS following bilateral infarcts in basal ganglia. For simplicity only one lead (Cz) is presented. Ticks on the amplitude axis indicate: 5 μV on A and B, 2 μV on C, D, and E. Ticks on the time axis indicate 200 ms in all graphics. The negativity is plotted upwards. More examples of ERP waveforms in PVS and MCS patients can be obtained from the corresponding author.

2.2. Group differences

The two main patient groups differed significantly only in the frequency of the MMN (4-field $\chi^2(1)=6.25$, $P<0.05$). Surprisingly however, it was the MG1 with a more severe diagnosis, which exhibited better MMN results. In contrast, the primary cortical component N1 was recorded more frequently in the MG2, but this difference was only marginally significant: $\chi^2(1)=3.56$, $P<0.10$.

Whereas the two main groups were rather similar, their differences from the respective control groups were substantial. Neither P3 nor semantic responses were found in any patient in the CG1. A striking exception was a female PVS patient with pronounced delta-activity in the EEG who showed significant N1 and MMN components and an apparent P3 which, however, did not reach our significance criterion (Fig. 3). Nevertheless, both N1 and MMN responses were less frequent in the CG1 than in the MG1: $\chi^2(1)=11.45$, $P<0.001$; and 10.47, $P<0.01$, for N1 and the MMN, respectively.

CG2 patients were superior to MCS patients with respect to the P3 responses in general ($\chi^2(1)=8.83$, $P<0.01$), in Oddball I and Oddball II ($\chi^2(1)=5.24$ and 3.89, respectively; both $P<0.05$). The differences in semantic ERP paradigms did not reach significance, but the percentage of patients having *at least one* semantic response was higher in the CG2 than in MCS patients: $\chi^2(1)=3.91$, $P<0.05$.

One might suggest that these results may have been influenced by the presence of patients with atypical

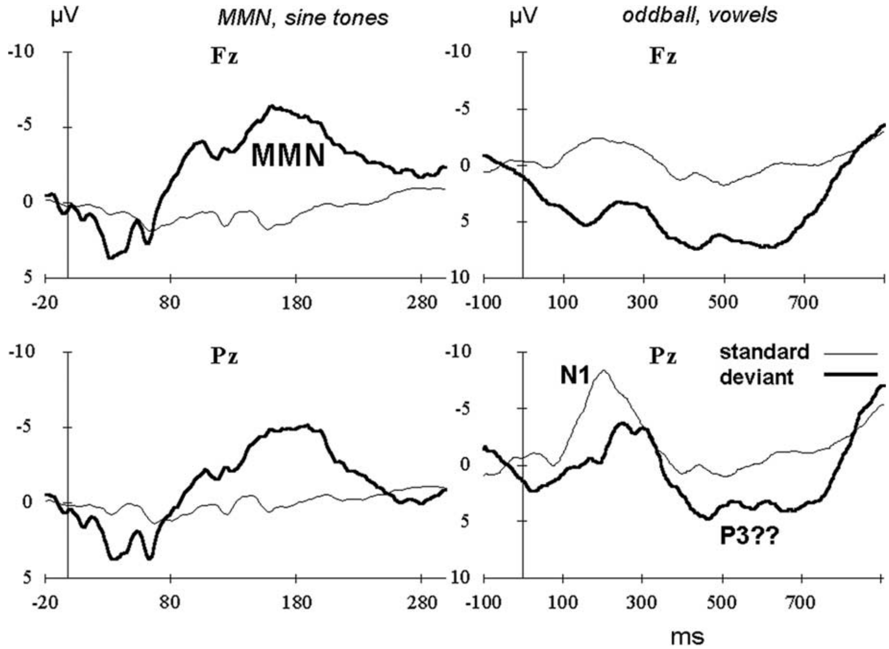

Fig. 3. ERPs of a female PVS patient (64 years, 7 months following brain anoxia) with a pronounced diffuse delta-activity in the rest EEG (CG1). Surprisingly, there was a significant MMN in the MMN experiment with two pure tones (left; $P=0.017$), a highly-significant ($P=0.001$) N1 in the oddball with two vowels, and an apparent P3-like deflection which, however, did not reach significance ($P=0.12$).

etiologies such as fat emboli and encephalitis. Thus the analysis was repeated with these patients being excluded (data in parentheses in Table 2). Again, the MG1 was better than the CG1 as regards the occurrence of N1 ($\chi^2(1)=15.45$, $P<0.001$) and the MMN ($\chi^2(1)=9.55$, $P<0.01$). The CG2 had a higher percentage of significant responses than the MG2 in Oddball I ($\chi^2(1)=16.15$, $P<0.001$) and Semantic oddball ($\chi^2(1)=4.56$, $P<0.05$). Likewise, the CG2 was superior to the MG2 in the percentage of patients who exhibited at least one significant P3 ($\chi^2(1)=6.41$, $P<0.02$) and at least one semantic response ($\chi^2(1)=4.61$, $P<0.05$).

The data are not essentially different if PVS versus MCS patients are compared regardless of their background EEG. Early cortical responses (N1, P2) are more frequent in MCS than in PVS: $\chi^2(1)=4.10$, $P<0.05$. The same is true for P3 responses in Oddball II (complex tones), but this difference only approaches significance: $\chi^2(1)=3.83$, $P<0.06$.

2.3. Temporal lobe lesion

Due to a large variability of pathomorphological findings in PVS and MCS patients, morphological data cannot be analyzed in full within the present article devoted to ERPs. However, the question can be risen as for how far the lack of an ERP component can be attributed to a focal brain damage rather than the clinical condition (i.e. PVS or MCS). The components P3, P600, and N400 are generated by complex networks containing frontal, temporal, and parietal sources, thus making difficult any simple prediction of the minimal morphological condition for these components. To the contrary, the components N1 and MMN are known to be strongly related to the activity of the auditory cortex, mainly in the temporal plane. CT data in our sample indicated 26 patients with lesions to the temporal lobe (15: predominantly right side; 11: predominantly left side). The MMN was present in 16 of these patients, which is a slightly lower rate as compared with patients without temporal lesion: χ^2 $(1)=3.12$, $P<0.10$, one-tailed. The significant N1 was found in 20 patients, which is not significantly different from the rest of the sample: $\chi^2(1)=1.52$, $P>0.5$.

2.4. Hierarchical processing

Simple versus complex stimuli. The comparison between the physical stimuli of different complexity (pure tones, chords, and vowels of human voice) has been reported in details elsewhere (Kotchoubey et al., 2001, 2003). In sum, the MMN and the P3 were both significantly better pronounced in response to musical chords than to simple sine tones. Including only those patients who showed a significant MMN or P3, the amplitude of the respective wave was smaller to sine tones than to other kinds of stimuli.

Simple versus complex information processing. As can be seen in Tables 2 and 3, middle-latency ERP components N1–P2, related to undifferentiated cortical processes, were observed more frequently than the MMN and P3 which presumably reflect more complex information processing. These latter components were found in about twice as many patients as significant responses to verbal stimuli. None of the patients without significant N1 exhibited any response to

Table 3
Relationship between outcome and etiology

	Total patients	Follow-up available	improved
Etiology			
Non-traumatic	56	34 (61%)	12 (35%)
Traumatic	34	12 (37.5%)	9 (75%)
Total	90	46 (51%)	21 (46%)

Patients with fat emboli, encephalitis, as well as with combined traumatic and hypoxic brain lesions are excluded.

verbal stimulation. This might be interpreted as a support for the hierarchical processing hypothesis.

However, an inspection of individual data shows that the hierarchical rules are not universal. Thus, the N1–P2 complex did not reach significance in 4 MG1 and two MG2 patients. However, 3 of these 6 patients demonstrated a significant MMN, and the other 3 exhibited a significant P3 (complex tones: 2 patients; voice: 1 patient). This means that every patient in the two main groups had at least one significant ERP response (Fig. 4).

Similarly, 6 of 54 patients without oddball P3 nevertheless demonstrated significant semantic responses (N400 to word pairs: 3 patients; N400 to sentences: 1 patient; N400 in both paradigms: 1 patient; late positivity in the semantic oddball: 1 patient). Moreover, two of these 6 patients did not show any MMN either.

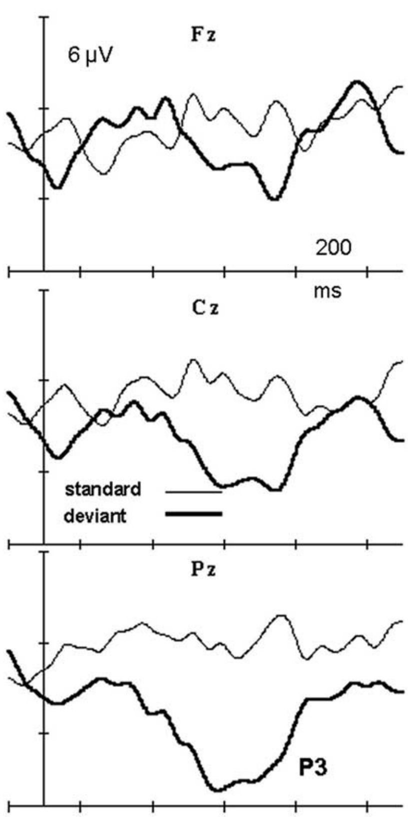

Fig. 4. A distinct and statistically significant ($P<0.01$) P3 in Oddball II despite the lack of N1 and P2 components, in an MCS patient (male, 55), 4 months after an anoxic brain injury.

2.5. Follow-up

Across all 4 patient groups, clinical improvement was observed more frequently in patients with a significant MMN than in those without the MMN: $\chi^2(1)=5.74$, $P<0.05$, see Fig. 5. The same tendency for the N400 approached significance ($P=0.079$). The correlation between the MMN and the 6-months outcome survived when taking into account all other variables related to the outcome: $t=2.12$, $P=0.044$.

Among PVS patients, clinical improvement was observed only in the MG1 (50%), whereas none of the CG1 patients improved. Further, there was a trend to a longer disease duration for patients who did not improve (mean 17.3 months) as compared with those who improved (mean 3.5 months): $t=2.03$, $P=0.054$. Also the variability of disease duration was higher in the non-improved (SD $=33.4$) than in the improved (SD$=2.2$; $F(21/24)=15.0$, $P<0.001$). No patient who was examined 1 year or longer after the accident improved in the following 6 months.

The improvement rate was higher in patients with traumatic head injuries than in patients with non-traumatic etiologies: $\chi^2(1)=5.64$, $P<0.05$ (see Table 3). The age difference between the improved (mean, 40.7) and not improved patients (mean, 44.8) was not significant ($t<1$). Also the clinical diagnosis was a poor predictor, as evidenced by the fact that the improvement rate was about 50% in both main groups. Even if we only consider patients with less than one year post ictum, the difference between the two groups is not significant: $\chi^2(1)=0.69$, $P>0.50$.

3. Discussion

3.1. Methodological issues

In this study, for the first time a large group of about 100 patients with PVS and MCS was investigated using the ERP technique. Also for the first time, a portable laptop system was used for EEG recording at the patient's bedside. Even though, for technical, clinical, and ethical reasons, not all data were collected from all patients, we were able to assess 93.3% of them.

To correctly evaluate the findings, we should take into account several factors that increase the probability to miss an ERP component really present in the data. Many of these factors, such as habituation, fluctuations in arousal, fatigue, latency jitter, etc., are discussed in details in our methodological article (Neumann and Kotchoubey, 2004). Additionally, an ERP component can be lacking due to a focal lesion to its cortical generator, irrespectively of the

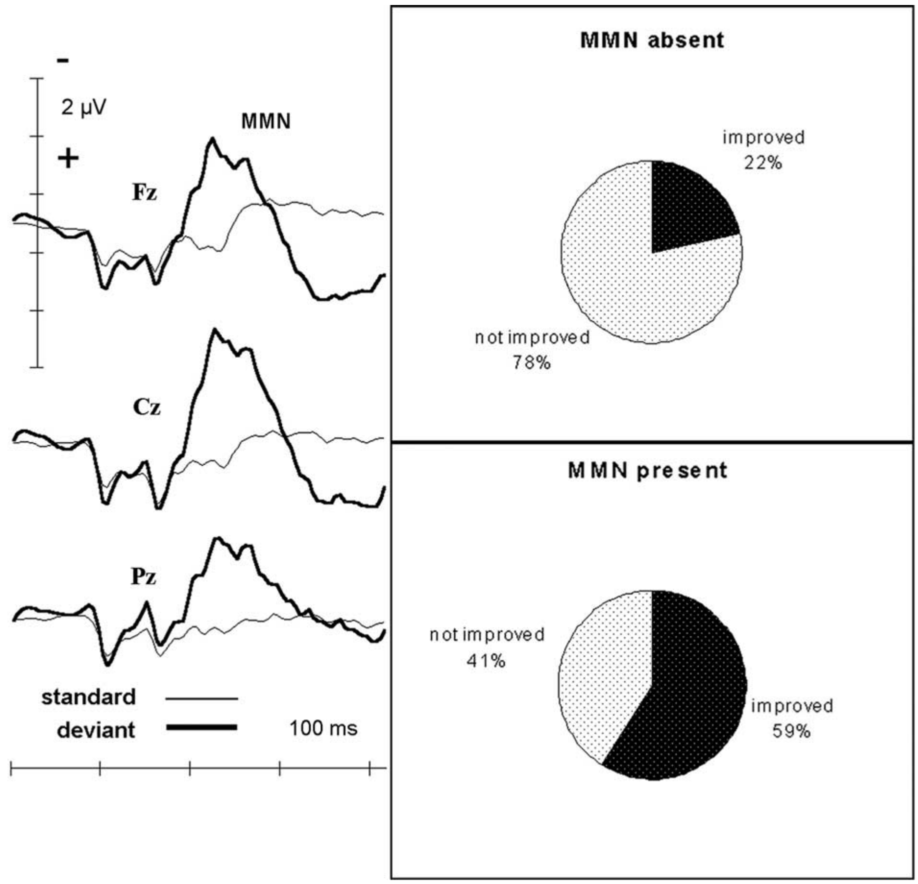

Fig. 5. Left panel: An example of a high-amplitude MMN to musical tones in a patient with a diagnosis MCS following head injury. The patient was discharged 3 months later with a considerable improvement. Right panel: Percentage of clinical improvement in patients with present versus absent MMN responses.

state of consciousness. The weak trend for patients with temporal lobe lesions to exhibit an MMN less frequently than patients without such lesions suggests that this possibility cannot be ruled out. On the other hand, the lateral temporal cortex, which is critical for two ERP components evaluated in the present study (N1 and MMN), is not an area typically damaged in PVS patients. Thus we observed all temporal lesions in CT (not only lesions of the lateral region) in less than 30% of PVS and MCS patients, and Kampfl et al. (1998a), using the more sensitive MRI technique, found lesions of the lateral temporal area in 14% of posttraumatic VS patients. Taking into account that most of these lesions were one-sided, diffuse, and did not look like a complete destruction of the cortical tissue, the importance of the local temporal damage as a possible cause for a lacking auditory N1 (or MMN) remains questionable. Even more difficult is the question about the importance of local cortical lesions, when it is applied to later components (P3, N400) generated by broadly distributed cortical networks. Which modules of those networks are critical so that their destruction leads to the disappearance of the corresponding ERP effect, should be investigated in a separate study.

To sum up, there are reasons to think that we may have underestimated the processing capacities of the examined patients. During the following discussion we should keep in mind that our ERP data across the whole sample are biased toward false negatives.

3.2. Cortical processes in PVS and MCS

Previous data cited in the Introduction have demonstrated that PVS patients can possess some level of cortical processing. The present results replicate and considerably extend those findings. In fact, we found that among patients with prevailing theta or slow alpha EEG background activity, *all* patients diagnosed as PVS exhibit some cortical responsivity. In some of them, only primary cortical components N1 and/or P2 were reliably proven. But more complex cortical responses were also present above chance in both main groups: the mismatch negativity was found in about one-half of these patients, an oddball-P3 in about one-third, and cortical evidence for semantic differentiation in about one-fourth of the patients. As discussed above, these numbers are probably underestimation.

Across all PVS patients, the ERP results were slightly below those for MCS patients. These differences, however, disappeared when MCS patients were compared with PVS patients with a comparable EEG pattern. This indicates that it might be useful to control for the background EEG whenever cortical processing functions of PVS patients are discussed.

This lack of differences between the two main groups of patients cannot be due to a low sensitivity of the ERP technique or to the small sample size. Were it so, the two control groups, small and heterogeneous, could not differ from the main groups as well. In fact, however, both CGs demonstrated highly significant differences. Most CG1 patients were almost non-responsive. In contrast, patients of the CG2 were considerably better than both MG1 and MG2. Six of the 10 CG2 patients had at least one semantic cortical response, a significantly higher percentage than that in the MG1 and MG2 (22–25%). These differences were obtained notwithstanding the severity of the lesions in many CG2 patients. Two of them displayed only minimal yes/no responses in communication and might even be diagnosed as MCS when using less strict criteria, broadly accepted in the literature (e.g. Phipps and Whyte, 1999; Piguet et al., 1999; Shiel and Wilson, 1998). However, these patients were not in MCS according to the most recent criteria (Giacino et al., 2002).

These data do not agree with those of Boly et al. (2004) who found a clear difference in cortical activation between PVS and MCS. In contrast to their findings, we obtained a greater-than-chance percentage of PVS patients having a P3 or P600, indicating activity in association cortical areas. It should be taken into account that neither Boly et al. (2004) nor other authors subdivided their PVS samples into subgroups with different levels of neurophysiological functioning. The highly significant differences between PVS patients with very severe versus only moderate disturbances in the background EEG underscores the importance of the activity of thalamo-cortical gating systems (Schiff and Plum, 2000) mediating neural mechanisms of perception.

The high frequency of cortical responses in PVS patients found in the present study can either be conceived of as indication of possible diagnostic errors (in line with Andrews et al., 1996; Childs et al., 1993), or as evidence that isolated thalamo-cortical circuits may be working in PVS patients indicating spared function of some specialized processing modules, although this processing is unrelated to conscious experience (in line with Plum et al., 1998; Schiff et al., 2000). Both accounts met difficulties, however. The former implies that a very high percentage of patients diagnosed as PVS are not in this condition. Moreover, it is related to a problematic assumption that imaging techniques directly measuring electromagnetic and metabolic activity of brain tissue can be more important in the diagnostics of PVS than clinical/neuropsychological assessment. The latter view is based on neuropathological (Gerstenbrand, 1987; Kinney and Samuels, 1994) and magnetic resonance evidence (Kampfl et al., 1998a) that diffuse axonal injury and lesions of the corpus callosum are more typical for PVS than lesions of the gray matter, and thus some cortical circuits may function in PVS patients as ‘islands’, separated from larger networks in which they are normally involved in healthy subjects. However, this ‘modular hypothesis’ has to specify what level of cortical activity would be sufficient to assume mental activity. Surely, even semantic processing can happen without conscious perception. Indeed, most ERP components can be obtained without subjective awareness (Yingling, 2001), but these unconscious effects are usually of a much smaller magnitude than those obtained in the present study (e.g. Shevrin, 2001); due to this small size such group effects are unlikely to be detected in individual patients, as reported here.

3.3. Outcome

It should be stressed that outcome prediction was not among the main goals of the present study. Some potentially important predictors were not considered, and, therefore, we avoided calculating multiple regressions given the sensitivity of these statistics to the set of input variables. Further, the patient sample in the present study was smaller and more heterogeneous than in the most successful prediction studies including 80–500 post-traumatic VS patients one to two months after the injury (Braakman et al., 1988; Danze et al., 1994; Kampfl et al., 1998b; Sazbon and Groswasser, 1990). Notwithstanding these differences, the present follow-up findings concur with the results of those studies in that the improvement rate was 46% (50% in the main groups), which corresponds to the mean rate obtained in the other studies. The shorter time post ictum and traumatic etiology were related to the better outcome. The lack of the effect of age is not surprising since this effect was also lacking in two big prognostic studies (Kampfl et al., 1998b; Sazbon and Groswasser, 1990). Electrophysiological data, i.e. the degree of impairment of the background EEG and the presence of the ERP component MMN, significantly correlated with the 6-month outcome. Although EEG is a routine examination in PVS, its prognostic value has, to our best knowledge, never been investigated before. Due to the interdependence between the possible predictors, one should be cautious in suggesting causal explanations. However, it should be mentioned that the MMN is one of the best predictors of emergence from acute coma (e.g. Fischer et al., 1999; Kane et al., 1998, 2000).

3.4. Hierarchy and its violations

The ‘hierarchic processing hypothesis’ was not supported by the present results. The assertion that the processing of simple stimuli would be more easy than that of physically complex stimuli, was disconfirmed. Complex musical tones elicited various ERP components (MMN, P3) consistently more frequently, and of a larger amplitude, than simple sinusoidal tones. This concurs with behavioral (Sundberg, 1991), electrophysiological (Tervaniemi et al., 2000) and neuroimaging data (Hall et al., 2002) on healthy human subjects, as well as with the data from animal studies (Rauschecker, 1997) that processing of harmonic tones is largely independent of the responses to single frequencies.

The second statement of the hierarchical hypothesis claimed that simple processing operations are necessary prerequisites for more complex operations. Average trends found in the present study were compatible with this idea. As a rule, patients' responses in simpler stimulation paradigms were more frequent than in more complex stimulation paradigms. However, this 'rule' was violated in at least 13 patients (13.4%). Different accounts on such exceptional but not very rare instances are possible. On the one hand, these hierarchy violations can be explained at the methodological level, e.g. by fluctuations of patients' arousal, leading to some experiments being performed in more, other experiments in less 'favorable' periods of time. Similarly, a large between-trials latency variance can critically affect middle-latency components, resulting in their disappearance in the average waveform, whereas a relatively slow P3 wave is less sensitive to this jitter. On the other hand, these paradoxical responses can be related to the above-discussed modular structure of cortical information processing in which singular encapsulated cortical modules in severely damaged patients are suggested to exist and work while disconnected from other modules (Schiff et al., 1999, 2000).

3.5. Clinical implications

Regardless of the interpretation, the above findings clearly indicate the necessity to use a whole battery of functional tests at various levels of complexity in every patient with severe brain injury. It is not enough to obtain a negative result, e.g. in an oddball task with two sine tones and, then, to declare a patient 'cortically non-responsive', as she can nevertheless demonstrate significant responses in more demanding tasks with more complex stimuli.

The set of stimulation paradigms used in this study can be regarded as a first draft of such a battery. More ERP-based experiments have been proposed during last years for the assessment of cognitive abilities in patients with severely damaged central nervous system. These included, for example, presentation of a patient's own name (Berlad and Pratt, 1995; Kotchoubey et al., 2004), nonverbal emotional exclamations (Bostanov and Kotchoubey, 2004), number sequences (Lang and Kotchoubey, 2002), as well as the development of ERP tests based on already existed and standardized neuropsychological paper-and-pencil tests (Byrne et al., 1995; Connolly and D'Arcy, 2000; D'Arcy et al., 2000; D'Arcy et al., 2003; Marchand et al., 2002). These paradigms were not systematically used in the present study—some of them because they require the ability to gaze fixation, which was lost in many our patients; others because the study started before these paradigms have been developed. On the other hand, several ERP paradigms used in clinical practice, such as oddball and MMN tests with sine tones, proved to be rather inefficient, and can probably be omitted in future investigation.

Further, the time to examine a waking PVS patient is usually limited due to many necessary therapeutical and rehabilitation procedures. Therefore, an investigator is necessarily involved in a difficult tradeoff between two goals: to obtain more information about different levels of a patient's brain functioning, or to obtain more reliable information by increasing the signal/noise ratio. Although there is no unique solution for this conflict, there are several ways to take its edge off. Simply increasing the number of trials may sometimes be useful, but it is neither the only possible nor the best way to improve the data quality, since too long examinations may result in missing an ERP effect due to the factors listed at the beginning of this discussion. Better opportunities would be provided by development of more reliable techniques of signal extraction (e.g. Bostanov, 2004; Kotchoubey et al., 2002), or cheaper and simpler recording facilities potentially available in each hospital (Hinterberger et al., 2005).

As a remote goal, a battery of neuropsychological stimulation procedures should be developed, aimed at various aspects of cortical processing and suitable for registration of both ERPs with their perfect temporal resolution and hierarchical organization on the one hand, and PET or functional magnetic resonance imaging with their excellent spatial resolution, on the other hand.

4. Conclusions

The hypotheses formulated in the introduction were only partially confirmed. The hierarchical processing hypothesis was, generally, not supported. This indicates that a patient's examination must not be terminated when the simplest cortical responses are lacking; this patient can nevertheless exhibit more complex responses. As expected, the low-level cortical processing was found in all MCS patients—but also in all PVS patients whose thalamo-cortical connections remained at least minimally preserved. The hypothesis was confirmed that MCS patients would frequently exhibit ERP components indicating complex information processing in association cortex; however, these components were also observed in a considerable number of PVS patients. Finally, a hypothesis aiming to validation of the ERP method stated that severely brain-damaged but conscious patients would demonstrate much more electrophysiological signs of intact cortical processing than PVS and MCS patients. This hypothesis was supported even though these control patients were just slightly better than MCS.

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