Background: A major challenge in the management of severely brain-injured patients with altered states of consciousness is to estimate their residual perception of the environment.

Objective: To investigate the integrity of detection of one’s own name in patients in a behaviorally well-documented vegetative state (VS), patients in a minimally conscious state (MCS), and patients with locked-in syndrome.

Design: We recorded the auditory evoked potentials to the patient’s own name and to 7 other equiprobable first names in 15 brain-damaged patients.

Results: A P3 component was observed in response to the patient’s name in all patients with locked-in syndrome, in all MCS patients, and in 3 of 5 patients in a VS. P3 latency was significantly (P<.05) delayed for MCS and VS patients compared with healthy volunteers.

Conclusions: These results suggest that partially preserved semantic processing could be observed in non-communicative brain-damaged patients, notably for the detection of salient stimuli, such as the subject’s own name. This function seems delayed in MCS and (if present) in VS patients. More important, a P3 response does not necessarily reflect conscious perception and cannot be used to differentiate VS from MCS patients.

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One of the most important clinical challenges in patients with severe brain damage is to estimate different aspects of their actual state of consciousness and, in particular, their residual conscious perception of the environment. Different methods have been developed to quantify the preservation of responses in the ascending sensory systems (especially the auditory and the somesthetic ways) and in the projection areas. Some of them seemed to be valuable clinical tools for prognostic evaluation. For example, analyses of short-latency event-related potentials (ERPs) revealed that somatosensory evoked potentials have a better sensitivity than brainstem auditory evoked potentials for the detection of brain dysfunction shortly after severe head trauma.1 Also, N1 and mismatch negativity of the long-latency auditory evoked potentials have been observed in patients with locked-in syndrome, demonstrating that the primary auditory cortex is still functional.2 The preservation of the primary auditory processing by cortical structures has also been observed by a functional neuroimaging study of patients in a vegetative state (VS).3 This study showed that while the resting metabolism of these patients was decreased, the auditory primary cortices (Brodmann areas 41 and 42) were still responding to the presentation of tones.

While previous studies suggest a relative preservation of the primary sensory processing, few have investigated the integrity of language comprehension in patients with severe brain damage. Long-latency ERPs to words offer the opportunity to explore semantic processing at the patients’ bedside. First, N400 potential is evoked in response to words that are semantically anomalous relative to a given context.4 However, this waveform is of low amplitude and, therefore, is not as easily identified in the electroencephalogram of severely brain-damaged patients, which is usually characterized by high-amplitude slow-frequency oscillations (in contrast to N400 ERP studies in conscious brain-damaged patients with, for example, aphasia after traumatic brain injury5 or stroke6). Second, a P3 (or P300) potential can be evoked in response to unexpected target.
words (presented in a sequence of multiple occurrences of a single word), notably when they are pertinent, such as for the subject’s own first name. However, the presence of a P3 wave in such paradigms could reflect either the recognition of the target’s intrinsic meaning or the detection of its acoustic salience (ie, the fact of being rare relative to a monotonous series) because the P3 amplitude is sensitive to task relevance and stimulus probability. For a review, see the study by Polich and Kok.9 To avoid this ambiguity, it has been proposed9 to remove the physical rarity of the target stimuli by using as sensory input a series of equiprobable first names among which is included the subject’s own name (SON). In these conditions, P3 presence becomes a valid neurophysiologic correlate of word semantic categorization.

Our current study explores the integrity of SON discrimination (independently of target occurrence probability) in severely brain-damaged coma survivors (those in a VS, those in a minimally conscious state [MCS], and those with locked-in syndrome [LIS]). Furthermore, we aimed to objectively assess, individually and at the bedside, the possible preservation of residual linguistic processing differentiating unconscious VS from MCS or LIS patients by an objective electrophysiological measurement.

METHODS

SUBJECTS

This study was prospectively performed in 18 right-handed severely brain-damaged patients classified according to internationally established criteria as being (1) in a VS,10 (2) in an MCS,11 or (3) affected by LIS.12 Only patients studied during awake periods, free of centrally acting drugs and without diagnostic ambiguity, were included for further analysis. Each data set composed cognitive ERP measurements and standardized clinical assessments of consciousness.

Fifteen patients (mean ± SD age, 54.9 ± 17.2 years) were included for further analysis (3 patients were excluded because of technical problems): 5 were in a VS (4 nontraumatic and 1 traumatic) (mean ± SD age, 51.8 ± 13.0 years), 6 were in an MCS (3 nontraumatic and 3 traumatic) (mean ± SD age, 58.5 ± 19.5 years), and 4 were affected by LIS (all nontraumatic) (mean ± SD age, 53.3 ± 21.9 years). (Table 1). All patients were right-handed, as evaluated by heteroanamnesis. None had a history of impaired auditory acuity. Somatosensory evoked potentials obtained by stimulation of the median nerve showed the presence of primary somatosensory cortex potentials (N20) in all patients. Five age-matched right-handed (Edinburgh inventory)13 healthy volunteers (2 women and 3 men; mean ± SD age, 54.6 ± 11.3 years) participated in the experiment. None of them had a history of audiologial or neurological disease. The experiment was conducted in agreement with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Written/eye-coded informed consent was obtained from all subjects or LIS patients or from a member of the patient’s family.

STANDARDIZED BEHAVIORAL EVALUATION

Before ERP measurements, an experienced neuropsychologist (C.S.) performed behavioral testing by the Glasgow-Liège Scale15 and the JFK Coma Recovery Scale–Revised.16 The Glasgow-Liège Scale combines the Glasgow Coma Scale17 with a quantified analysis of brainstem reflexes: fronto-ocular, vertical oculocephalic, pupillary, horizontal oculocephalic, and oculocardiac.15 The Glasgow-Liège Scale is calculated as the sum of eye opening, motor response, verbal response, and brainstem reflex subscores, and is scored from 3 (worst) to 20 (best). The JFK Coma Recovery Scale–Revised is a recently validated behavioral scale that explicitly incorporates the diagnostic criteria for VS10 and MCS11 into its administration and scoring scheme, and is unique in allowing the derivation of a diagnostic directly from the examination findings.18 It includes auditory, visual, motor, oromotor/verbal, communication, and arousal subscales, and ranges from 0 (worst) to 23 (best). Following ERP recordings, neurobehavioral evaluation continued for VS and MCS patients twice a month to increase diagnostic certainty.

STIMULATIONS

We elaborated 6 sequences of 80 stimulations containing 8 first names, 1 of them always being the SON. Only this name changed for every subject, the 7 other first names (OFNs) being the same for all participants. The OFNs were selected from a previous study19 as a series of first names of similar high frequency of use in the French language. For each sequence, each name was presented 10 times in random order, thus making a complete series of 80 equiprobable first names (probability, 12.5% for each name), with an interstimulus interval varying between 130 and 1400 milliseconds. After each recording session, the subject or the subject’s family was asked whether 1 of the other names had a particular emotional importance (ie, they corresponded to names of close relatives). If it was the case, the name was excluded from the ERP analysis. All first names were disyllabic, were recorded by the same neutral male voice (F.P.), and were digitized and replayed binaurally at a 90-dB sound pressure level maximal intensity.

ERP ACQUISITION

For patients, data were acquired at their bedside. Preceding each electroencephalographic recording, the behavioral status was evaluated by the JFK Coma Recovery Scale–Revised20 and the Glasgow-Liège Scale.15 Control subjects were studied while laying in bed with minimal ambient noise. Electrodes and mini-earphones were put in place. The electroencephalographic signals from 3 electrodes, Fz, Cz, and Pz (placed according to the International Ten-Twenty System),21 referenced to the nose; the electro-oculogram, from 2 electrodes diagonally above and below the right eye; and the electromyogram, from 2 electrodes on the chin were amplified (×150 000) and sampled at 300 Hz by an acquisition system (NuAmps; NeuroSoft, Sterling, Va) with an analog bandpass of 0.1 to 70 Hz (except for the electromyogram where the bandpass was 10-100 Hz). A ground electrode was placed near Fz, and impedances were kept below 5 kΩ. The subjects heard, eyes closed, 6 series of 80 equiprobable first names, without any specific task (ie, passive condition).

ERP ANALYSIS

Event-related potentials were averaged according to the type of first name (SON vs OFN) and the electrode position (Fz vs Cz vs Pz). Before averaging, single epochs with an amplitude of 30 μV or higher or those containing eye movements or electromyographic artifacts were excluded from averaging. A different number of trials between SON and OFN may
bias our obtained results because of signal-noise ratio differences. To address this concern, separate OFN averages were constituted, each containing a similar number of trials as the SON average. Comparisons between separate OFN and SON averages confirmed results obtained with grand averages of OFN data, validating our reported results. For illustrative purposes, grand-averaged ERPs were constructed for all control subjects and for each clinical entity (VS, MCS, and LIS).

Statistical calculations were performed on averaged traces from individuals: amplitudes (from baseline) and latencies of the 4 predominant components, labeled N1, P2, N2, and P3, were calculated for individual averages. If the P3 component was not well defined (this being the case after OFN or after...
SON for certain patients), we chose the maximum amplitude (and its associated latency) in a temporal window predefined on grand-averaged ERPs. Amplitude values were tested with a multivariate analysis of variance (MANOVA) with repeated measures on component (N1 vs P2 vs N2 vs P3), name (SON vs OFN), and electrode position (Fz vs Cz vs Pz). Latency values were tested with a MANOVA with repeated measures on component (N1 vs P2 vs N2 vs P3) and name (SON vs OFN). The independent variable was the group (control, MCS, VS, and LIS). The MANOVAs were subjected to a Greenhouse-Geisser conservative df correction. A Tukey comparison with a threshold at \( P < .05 \), and corrected for multiple comparisons, was performed when significant interactions emerged on MANOVA.

In addition to the visual inspection and interpretation of the data, a statistical analysis tested in each subject the significance of the P300 to the SON compared with the OFN. Adopting a similar approach as Marchand et al., individual waveforms were analyzed on a point-by-point basis using serial \( t \) scores, which take into account the variance of the individual electroencephalographic trials composing the grand-averaged ERP. \( t \) Scores were computed for all subjects in a temporal window of 50 milliseconds around the peak latency of the P300. Results were considered significant at \( P < .05 \).

### RESULTS

In healthy controls, the SON evoked the classic N1, P2, N2, and P3 components at about 150, 230, 305, and 460 milliseconds, respectively (Table 2 and Figure 1). The ERP latencies were delayed compared with those reported in the literature because the population of our study was older; this effect being previously well documented.

Among the patients, in all but 2 cases (patients 3 and 4, both in a VS), well-defined ERP components were obtained in individual averages (Figure 2). Notably, a P3 component was clearly observed after the SON in all patients affected by LIS and in an MCS, and in 3 of 5 patients in a VS (Figures 1 and 2). The individual statistical P300 analysis showed significant \( t \) scores \( (P < .05) \) for all subjects, except for 2 VS patients (patients 3 and 4) and 1 LIS patient (patient 13). The LIS patient failed to show a significant P300 \( (P = .06) \), probably owing to the recording having many artifacts and the ensuing insufficient statistical power (because of uncontrollable cervicofacial muscle contractures, only 13 valid trials could be obtained for the SON in this case).

The MANOVA did not show any significant \( (P = .65) \) group effect on ERP amplitudes. In contrast, the analysis demonstrated that the interaction between component and name had a significant effect on ERP amplitudes \( (F_{3,48} = 26.53, P < .001) \). Post hoc analyses revealed, as expected, that P3 amplitude was significantly higher in response to SON than to OFNs for all groups \( (P < .05) \) (Table 3). No significant differences \( (P > .05) \) were observed for the other components.

With regard to latencies, the MANOVA showed a significant group \( \times \) component interaction \( (F_{5,48} = 3.5, P = .01) \). Post hoc analyses revealed that P3 latency was significantly delayed for the VS group compared with the LIS group and controls, and for the MCS group compared with the controls (Table 2). No significant differences \( (P > .05) \) were observed for the other components.

### COMMENT

It is not surprising to observe a differential P3 wave in LIS patients because it can be expected that their cognitive functions, and notably their linguistic comprehension, remain preserved, even if their bedside cognitive neuropsychological testing remains challenging.

For MCS patients, our results extend those of Boly et al. and Schiff et al., who suggested that the auditory system of these patients was relatively well preserved in response to passive tones and language stimulation, respectively. The emergence of a P3 wave to the SON (compared with OFNs) suggests that MCS patients are able to detect salient words. However, the significant difference in P3 latency compared with controls shows that this word processing is delayed in the MCS group.

The many behaviorally well-documented VS patients emitting a differential P3 was somehow unexpected. Previous studies have reported fewer unconscious patients emitting a P3 to deviant (and rare) tones. Yingling et al., Harris and Hall, Gott et al., and Mut-schler et al. were able to record P3 components in 22% to 30% of comatose patients (2 of 9, 2 of 8, 6 of 20, and 6 of 20 patients, respectively). Similarly, Glass et al. have recorded a P3 response using an ordinary oddball paradigm in 38% (3 of 8) of patients thought to be in a VS. The emergence of a P3 response in 3 of 5 of our VS patients might be because of the quality of the implicitly targeted stimuli (ie, the SON), which was highly salient because of its obvious emotional dimension and its familiarity. Accordingly, Signorino et al have shown that emotional stimuli increase the chances of obtaining a P3 response in comatose patients. These researchers used a conventional oddball paradigm and an oddball paradigm in which the tones were coupled to emotional verbal stimuli (ie, a short phrase spoken by a member of

### Table 2. Data for N1, P2, N2, and P3 Latencies in Response to the Subject’s Own Name for Each Clinical Entity

<table>
<thead>
<tr>
<th>Group</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those in a VS</td>
<td>191.2 ± 33.7</td>
<td>332.8 ± 30.2</td>
<td>475.6 ± 26.5</td>
<td>762.4 ± 35.2</td>
</tr>
<tr>
<td>Those in an MCS</td>
<td>178.4 ± 14.4</td>
<td>268.4 ± 29.6</td>
<td>423.6 ± 36.2</td>
<td>711.2 ± 57.8</td>
</tr>
<tr>
<td>Those with LIS</td>
<td>151.0 ± 9.7</td>
<td>202.5 ± 9.1</td>
<td>296.5 ± 16.7</td>
<td>531.0 ± 52.7</td>
</tr>
<tr>
<td>Controls</td>
<td>148.4 ± 5.0</td>
<td>232.4 ± 19.3</td>
<td>306.8 ± 27.0</td>
<td>460.6 ± 33.7</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.

*Data are given as mean ± SE milliseconds.

†\( P < .05 \) compared with controls.
the family or the patient’s name) and obtained a P3 in 38% (6 of 16) of comatose patients in the first condition and in 56% (9 of 16) of comatose patients in the second condition. Our study further suggests that salient stimuli, such as the SON, can induce linguistic processing in some clinically well-documented VS patients, although delayed compared with age-matched controls. However, the absence of significant differences between the VS and MCS groups indicates that the P3 response cannot be used to differentiate VS from MCS or LIS patients. These data emphasize the importance of complementary (nonbehavioral) investigations in the assessment of residual cognition in noncommunicative brain-damaged patients. Patients in a VS are not “apalic” or in “neocortical death.” The VS is a more heterogeneous clinical entity than previously thought, and VS patients may show preserved islands of functional “pallium” or neocortex. Our findings are also concordant with recent functional neuroimaging work of Schiff et al and Owen et al, showing that islands of cerebral function may be preserved in some—but not all—VS patients.

Our results raise several questions. First, which characteristic of the SON stimulus accounts for the brain’s P3 response? Is it familiarity (high frequency of exposure during the entire lifetime) or emotional value? Indeed, the SON is a piece of information that we often process since infancy, and it is usually considered to be emotionally charged. Recent work suggests that, in healthy subjects, the emotional charge of the SON per
It may not be sufficient to grab attention. Thus, it would be useful to evaluate whether a differential P3 component is also recorded when emotional words, rather than the SON, are presented to LIS, MCS, and VS patients.

A second question relates to the conscious perception of the SON. Because the elicitation of a P3 wave is not necessarily concomitant to a phenomenal consciousness (it is also evoked during unconscious subliminal perception), we would rather limit the interpretation of the observed P3 response in some of our VS patients as an index of partially preserved, albeit restricted, cerebral processing for “automatic” speech comprehension. As suggested by Dehaene and Naccache, phenomenal consciousness is probably the consequence of a coherent activity involving structures distributed throughout the brain. Thus, one way of assessing if noncommunicative patients are aware of external stimuli would be to search for stimulus-induced neural synchronizations using adapted electrophysiological measures.

A last question involves the prognostic significance of a P3 response to presentation of the SON. The few patients who underwent evaluation in the present work...
leaves this question open. None of our 5 VS patients subsequently recovered consciousness, and only 1 of the 6 MCS patients showed good recovery 1 year after brain injury. Future investigations in an extended population of patients would help to determine whether this differential P3 response indicates a higher probability of recovery.

In conclusion, to our knowledge, this study is the first to show that a differential P3 component could be recorded in response to the SON, compared with OFNs, in a small but behaviorally well-documented group of MCS and LIS patients (6 of 6 and 4 of 4 patients, respectively) and in some (3 of 5 patients) in a VS. Because we used stimuli that were equiprobable words, the obtained P3 responses can be interpreted as an index of some preserved semantic processing, independently of the probability of occurrence of the stimuli. Our data demonstrate that a P3 response does not necessarily reflect conscious perception and cannot be used to reliably differentiate individuals in a VS from those in an MCS.

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Additional Information: Drs Laureys and Maquet are FNRS research associate and research director, respectively.

<table>
<thead>
<tr>
<th>Group</th>
<th>N1 (at Cz)</th>
<th>P2 (at Fz)</th>
<th>N2 (at Pz)</th>
<th>P3 (at Pz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those in a VS</td>
<td>−4.7 ± 1.3</td>
<td>1.7 ± 0.3</td>
<td>−4.3 ± 1.8</td>
<td>5.1 ± 1.1</td>
</tr>
<tr>
<td>Those in an MCS</td>
<td>−2.1 ± 1.0</td>
<td>1.4 ± 0.4</td>
<td>−4.1 ± 1.2</td>
<td>7.3 ± 1.6</td>
</tr>
<tr>
<td>Those with LIS</td>
<td>−1.3 ± 0.7</td>
<td>1.7 ± 0.6</td>
<td>−3.9 ± 1.8</td>
<td>6.3 ± 1.9</td>
</tr>
<tr>
<td>Controls</td>
<td>−6.0 ± 0.6</td>
<td>2.0 ± 0.9</td>
<td>−2.2 ± 1.5</td>
<td>9.9 ± 3.7</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.

*Data are given as mean ± SE microvolts.

REFERENCES


