Is there a Mind? Electrophysiology of Unconscious Patients

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Event related brain potentials (ERPs) provide information about cortical processing in severe neurological patients whose cognitive abilities cannot be expressed in their behavior. In coma, ERPs contribute to the prediction of the outcome. In a vegetative state, ERPs uncover the functional state of cortical processes. The significance of ERPs in the neurophysiological study of consciousness is discussed.

The question of whether patients who appear to be unconscious are really without conscious experience has remained an enigma until recently. Numerous anecdotes exist about seemingly unconscious patients who, in fact, were able to perceive their environment (4). One may reformulate this question in physiological terms by asking to what extent cortical functions are preserved in neurological patients with severe global brain injury or in other unresponsive persons. A technique allowing us to test those covert cortical functions are event-related brain potentials (ERPs).

ERP methodology

Electroencephalogram (EEG) waves time-locked to particular events, like sensory stimulus or a patient’s motor response, are referred to as evoked potentials. They can be roughly subdivided into two classes. Those of the first class, early, short-latency components (several milliseconds to several tens of milliseconds after stimulus), reflect propagation of sensory signals from receptors via ascending pathways to the cortex. Some of them are widely used in clinical neurophysiology (see Ref. 10). However, these short-latency waves merely indicate whether sensory pathways are intact. They do not convey information about cognitive processes, and thus they are irrelevant to the issue of consciousness.

The other group of evoked potentials is referred to as ERPs. In contrast to the short-latency waves described above, ERPs are of cortical origin. Of special importance are ERP waves that appear between 100 and 1000 ms after stimulus. ERPs constitute a unique, noninvasive technique to obtain information about how the cortex processes signals and prepares actions. In general, what is observed when a patient performs a neuropsychological test is always a result of many physiological processes. ERP waves are supposed to “manifest” single components of this processing chain. The ERP method permits us to follow stimulus processing in real time at all levels of complexity.

ERPs can be used to study the processing of physical stimulus features as well as the processing of semantic stimulus features (language, meaning). Regarding the former, the most frequently used experiment is the oddball paradigm (5) in which rare (e.g., 20%) stimuli (“targets”) are randomly inserted in a sequence of frequent (e.g., 80%) stimuli and the subjects’ task is usually to count the rare events (Figs. 1A and 2). Sometimes, albeit smaller, effects are observed without the counting instruction: the so-called passive oddball (15).

Sometimes, both frequent and rare stimuli are presented to two sensory channels (e.g., the right and left ears). Only the rare stimuli in one of the channels (the relevant channel) serve as targets; stimuli in the other channel should be ignored. This paradigm has allowed researchers to identify several robust ERP phenomena, which are best studied by using a subtraction technique (17). Thus the subtraction of the ERP to frequent stimuli in the irrelevant channel from those to frequent stimuli in the relevant channel reveals a negative wave, sometimes called “processing negativity,” which starts as early as 50-100 ms after stimulus presentation. In the auditory modality, the subtraction “rare minus frequent” within the irrelevant channel results in a “mismatch negativity” (MMN; Ref. 17). Finally, the difference between rare targets and nontargets in the relevant channel is dominated by a large parietal wave with a latency of 350–500 ms; this wave, referred to as P3b or P300, is often preceded by a brief negativity (N2; Fig. 1).

The second type of cognitive analysis, the processing of semantic input, is frequently assessed by means of sentences that either end in a semantically correct fashion or have inappropriate endings (14). The final words contradicting the semantic context elicit a large parietal negative wave (N400). Alternatively, the semantic context can be construed by using pairs of words that are either strongly associated or unrelated to each other (2). Oddball techniques can also be used for assessment of semantic comprehension. For example, subjects are presented words of different semantic classes. Words belonging to one of these classes should be counted, the other words ignored. Like in oddball tasks with tones, the rare targets elicit a parietal P300 wave but with a longer latency.

The negative waves recorded on the scalp are most probably a result of summation of numerous excitatory postsynaptic potentials in the apical dendrites of cortical units (layers I and II) and thus reflect threshold lowering of pyramidal neurons and their preparation for future activity. The positive waves are supposed to result from depolarization processes in deeper cortical layers and thus to reflect the actual work of underlying cortical areas, i.e., the consumption of the resources prepared during the preceding negativity phase.
Evoked potentials and ERPs in coma

Coma is the most severe disorder of the functions of the central nervous system, resulting usually from a dysfunction of midbrain structures regulating wakefulness. Coma is always an acute state indicating an ongoing pathological process caused, e.g., by trauma, anoxia, inflammation, or hemorrhage.

Short-latency evoked potentials (<50 ms) are frequently used for the prediction of the outcome from coma. Characteristically, they show a very low rate of false negative predictions (i.e., most patients missing these waves show a negative outcome, e.g., death). On the other hand, the rate of false positive predictions is high (i.e., well-preserved brain waves are recorded in patients who have a bad clinical prognosis). Clearly, because these early waves reflect rather primitive processing operations, their being intact only indicates that simple sensory processes are possible; in this sense, they can overestimate the patient’s state.

Some ERP-based inferences are related to the contemporary knowledge about the functional meaning of particular waves. For instance, a frontal P3a wave in oddball (Fig. 2D) is interpreted as reflecting more shallow stimulus processing compared with a parietal P3b (Fig. 2E), since P3a is usually regarded as a rather automatic phenomenon. Although much evidence has been accumulated to support this interpretation, these notions of the parietal versus frontal varieties of P3 may change with future research. But this hypothetical knowledge can nevertheless lead to inferences that are impossible if only a behavioral response is recorded.

In other instances, interpretation of clinical ERP research is theory-free. Thus when a patient should count words belonging to a particular class, a P3 response to these words proves the patient’s ability for semantic classification regardless of what the exact functional meaning of this P300 might be. This is because a classification process is conditio sine qua non a differential brain response; if the patient were unable to classify, no P300 to a particular word class could appear (Figs. 1D and 2F).

The situation changes when we pass to ERPs. To date, few large studies on patients in coma have been carried out, and all of them used ERPs recorded in a passive oddball paradigm with simple sine tones (6-8, 10, 16). In sum, these studies yielded two main results. First, the ability of the cortex to differentiate between frequent and rare events could be detected in many coma patients (an estimate of 30–50%). Second, when ERP findings are compared with the outcome of coma, the rate of false positive predictions is very low, sometimes equal to zero, whereas the rate of false negative predictions (i.e., the outcome is better than predicted on the basis of ERP data) is high, the only exception being a study of 20 anoxic coma patients in which a false positive rate of 50% was found (16). Furthermore, ERP components related to more complex cognitive processes (i.e., MMN or P3) yield a higher false negative rate and a lower false positive rate than components such as N1 and P2 reflecting the first cortical reaction to a stimulus. This indicates that ERP tests are biased to underestimate patients’ cognitive abilities. Different factors can contribute to this underestimation. First, ERP components are also occasionally absent in a few healthy subjects; hence, although the presence of a particular ERP effect always suggests the presence of the corresponding function, its absence does not prove the lack of this function. Second, many neurological patients have considerable fluctuations of arousal, and a neurophysiological test may be carried out at the moment of arousal decrease or some time earlier or later the same patient would demonstrate a better outcome. Third, a test run may last too long, and its result may be negative not because the patient cannot distinguish between the presented stimulus categories but because he or she cannot concentrate for this time period. Fourth, the technique of ERP averaging implies that the particular brain wave not only occurs but is also time-locked throughout testing; a large latency jitter may lead to the disappearance of the wave in the average although it was present in most single trials. Fifth, statistical tests performed to confirm the existence of the wave are generally biased to retain the null hypothesis (H0, which reads that the patient does not distinguish between the presented stimuli) until it is very improbable. This means that
the conventional statistics, with their reasonable conservatism, are directed against the patient. At present, therefore, the ERP test data should probably be treated as the lowest limit of the patient’s capabilities, even though these data show that many more patients are capable of higher cortical information processing at different levels than may appear to be the case on the basis of clinical-behavioral observations.

“Waking coma” is not coma

Some patients surviving coma pass to another condition called the vegetative state (VS). In contrast to coma, midbrain functions are largely preserved in VS, which is manifested in a preserved sleep-wakefulness cycle. Also, subcortical reflexes to simple stimuli like flash or sound are preserved. However, all cortical functions are, by definition, completely lacking (13), which gave rise to the description of VS as “waking coma.” Another important difference from coma is that VS can exist both as an acute pathological state (transition from coma to another syndrome) and as a residual condition after a brain disease has already done its work, leaving a mass of destroyed cortical neurons.

These differences determine different strategies in ERP studies. The diagnosis of coma, with its almost complete nonreactivity, is usually simple, and the critical issue, addressed by ERP studies, is that of prognosis. In contrast, the diagnosis of VS sometimes requires very subtle differentiation between subcortical and cortical, “simple” and “complex” responses, resulting in a high diagnostic error rate (1, 3). Particularly difficult may be the differentiation from “locked-in syndrome,” in which (usually after a stroke in the anterior part of the pons cerebri or as a result of degeneration of motor neurons in the motor cortex and/or spinal cord) a patient becomes completely or almost completely paralyzed. Although cognitive functions can largely remain intact in this condition, the patient cannot express these functions due to the lack of motor control (18). The difficulty of differentiation between the two states is further enlarged by the fact that there are numerous transitional conditions between VS and locked-in-syndrome. In this case, the prognosis, therapy, and rehabilitation measures depend on the correctness of the diagnosis.

ERPs in VS

In contrast to coma, ERPs have only sporadically been used for assessment of cognitive abilities in VS. One of these studies (20) used several procedures addressing different levels of processing complexity. No ERP response was obtained in 11 out of 43 patients with “definite VS” but in only 1 of 23 patients qualified as “questionable VS.” In another recent study (9), the N1 and MMN ERP components were recorded in response to changes in complex tonal patterns (e.g., the change from oboe to clarinet) in 10 nonresponsive postcomatose patients (probably in VS). Eight out of ten patients showed no clear cortical wave. These data left some doubt as to whether consistent ERP responses can be recorded in VS at all.

We examined 34 patients with severe brain damage. All of them had normal early acoustic evoked potentials, suggesting that primary auditory pathways were intact. Most patients had general EEG slowing, with prevailing rhythms of 5–7 Hz but none exhibited dominant delta activity. Seventeen patients were diagnosed as typical VS (i.e., nonresponsive); the other 17 patients showed inconsistent responses to commands and were qualified as “minimally responsive.” VS was caused by a traumatic brain injury (15 patients), acute brain anoxia (10 patients), stroke (8 patients), and encephalitis (1 patient).

A broad range of ERP tests was employed at the patient’s bedside, including different versions of oddball and semantic match/mismatch paradigms. In addition to visual evaluation of the ERPs by two raters (as in Ref. 9), a statistical comparison between the two conditions in each test (e.g., target vs. standard in oddball tasks; related vs. unrelated words in the word pair task) was performed on the basis of a single-trial analysis (12).

According to visual inspection of ERP waveforms, 25 out of 34 patients had a P3 wave in at least 1 of the 3 oddball tests (sine tones: 9, complex tones: 11, vowels: 16). Furthermore, 11 waveforms indicated semantic differentiation in at least 1 of the tests (semantic oddball, word pairs, and sentences). With more conservative criteria were used, the corresponding numbers were 15–20 patients with a clear P3 response to physical stimuli (sine tones: 4–6 patients; complex tones: 9–11 patients).

**FIGURE 2.** A–E: varieties of ERPs in an oddball paradigm (with 2 musical tones) in severely brain-damaged patients. A: lack of cortical response in patient with hypoxic brain injury. B: distinct ERP consisting of the P1, N1, and P2 components (but without any differentiation between standards and targets) in a patient with head trauma. C: cortical negativity in response to rare targets (here in patient with multiple subcortical strokes) is regarded as superficial differentiation between 2 stimuli. D: positive wave with frontal maximum and peak latency of 250–300 ms (P3a) may be conceived of as a manifestation of orienting response to rare tones (another patient with severe head injury). E: normal response pattern, here recorded in patient with “locked-in syndrome” caused by a pontine stroke. F: well-preserved P600 response to semantic oddball task in a young female patient who remained almost unresponsive for 1 year after a massive hemorrhage in all ventricles that followed a seemingly successful tumorectomy.
vowels: 5–7 patients) and 10 patients who were capable of semantic processing.

For the above-stated reasons, these figures underestimate the real state of affairs. This means that one- to two-thirds of patients with suspected VS were capable of cortical differentiation of physical stimulus features and that at least 20% of these patients differentiated semantic stimuli (i.e., their brains comprehended language). The P3 wave was better pronounced in patients with minimal behavioral responses than in those whose behavioral responsiveness was completely lacking. However, even in the latter group P3 was found in nine patients. Furthermore, no difference between the minimally responsive and nonresponsive groups was found in semantic tests: at least three “nonresponsive” patients did differentiate responsive and nonresponsive groups was found in semantic processing.

Increasing the reliability of ERP assessment

Whenever a reliable difference is obtained between the cortical responses, e.g., to words versus pseudowords or to related versus unrelated words, such difference supports the assumption that the brain does distinguish between the corresponding stimulus classes and, hence, is able to perform some operations necessary for perceiving and understanding speech.

This emphasizes the importance of inferential tests for individual ERP waveforms. If a reliable response indicates that the corresponding function is preserved, the issue of response reliability becomes crucial. In ERP studies of coma and VS conducted to date, this issue has not received sufficient attention. Most researchers simply relied on visual inspection of the waveforms (16, 20). Some check the consistency of the visually detected waves using a cross-correlation between independent subaverages (6) or between two consecutive recordings (8). Others compare ERP waves with similar waves observed in healthy subjects (11). The different methods for assessment of whether the relevant wave was present or absent in a given patient’s waveform can explain the variability of results reported in the literature.

Clearly, we cannot restrict ourselves to visual judgment of ERP waveforms any longer. But the standard quantitative approach to ERP assessment is problematic too. In this approach, component amplitudes and/or latencies are measured within time epochs of interest that are previously selected on the basis of visual inspection of the waveform. This preprocessing the statistical estimation. An alternative is a multivariate approach in which the entire ERP curve enters the statistical analysis. Most ERP paradigms used in coma and VS entail two conditions (e.g., standards vs. targets and appropriate vs. inappropriate words). The EEG data points in the two conditions can be compared by means of Hotelling’s test.

Figure 3 shows ERPs of two VS patients in the word pair paradigm. In both cases, the waveforms for semantically congruent versus incongruent words appear to differ at some locations but not at others. It is difficult to find a particular “wave” clearly distinguishing between the two conditions, which poses a huge problem for a univariate test. In patient A, the attempts to test the visible difference in the mean amplitude over several selected time windows and electrode locations yielded nonsignificant results. In patient B, the curves were found to differ over the frontal cortex within a preselected interval of 480–930 ms. The multivariate T²-test performed with wavelet approximated data (to reduce the number of variables) results in significant between-condition differences for both patients.

It should be emphasized that the analysis included an interval of 300–812 ms, which was not selected on the basis of previous visual inspection of the data.

Conclusions

Evidence from ERP research suggests that many patients diagnosed as in coma or VS are able to perceive and process various aspects of their environment, including, in some cases, semantic elements of human speech. Although this technique still needs to be refined and is not yet capable of exact assessment of each individual patient’s abilities, it is already clear that higher cortical functions are preserved in many patients who cannot express their abilities in their behavior. The identification of “consciousness” with “rational expressive behavior” that originates in folk psychology does not hold any longer, since people who cannot control their behavior can nevertheless perform cognitive operations of different levels of difficulty.

ERPs reflect widespread sequences of different cognitive operations. Even though these operations may or may not be
strongly related to conscious experience, their presence always indicates that a brain mechanism necessary for that operation which is required for the attribution of significance (“understanding”) is intact. An argument that ERP differentiation between semantic stimuli does not prove the conscious differentiation in meaning presumes a qualitative difference between the neural substrates of conscious and unconscious processes. This assumption does not find support in the empirical data. Rather, conscious and unconscious processing of verbal material employs largely overlapping brain structures, with conscious processing probably involving more cell assemblies of the same type simultaneously (19). The continuum between nonconscious and conscious processing is fluid; no exact borders can be drawn. The vagueness of these constantly moving borders does not allow conclusions, which may imply a negative clinical bias.

Consciousness is a heterogeneous concept, both philosophically and physiologically. Several physiological conditions in diverse brain systems have to be fulfilled before conscious awareness is possible. Some of these diverse physiological conditions are known, including arousal of cortical neurons by cholinergic reticular fibers; activation of the reticular thalamus, specific thalamic nuclei, thalamocortical and prefrontothalamic connections; reentrant loops between primary and secondary cortical areas; and coherent cortical dynamic binding of cell assemblies by fast intracortical oscillations.

ERPs constitute only one of several possible windows into those processes and areas involved in the production of conscious experience. Thus reticular and thalamic activation would need careful measurement of blood flow changes using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). However, both techniques are pos

### References


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