

# Cognitive Event-Related Potentials in Comatose and Post-Comatose States

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**Abstract** We review the interest of cognitive event-related potentials (ERPs) in comatose, vegetative, or minimally conscious patients. Auditory cognitive ERPs are useful to investigate residual cognitive functions, such as echoic memory (MMN), acoustical and semantic discrimination (P300), and incongruent language detection (N400). While early ERPs (such as the absence of cortical responses on somatosensory-evoked potentials) predict bad outcome, cognitive ERPs (MMN and P300) are indicative of recovery of consciousness. In coma-survivors, cognitive potentials are more frequently obtained when using stimuli that are more ecologic or have an emotional content (such as the patient's own name) than when using classical sine tones.

**Keywords** Coma · Vegetative state · Minimally conscious state · ERPs · N100 · MMN · P300 · N400

## Introduction

Survivors of severe traumatic or hypoxic-ischemic brain damage classically go through different clinical entities before partially or fully recovering consciousness. Consciousness is a multifaceted concept that can be divided into two main components: arousal (i.e., wakefulness, or

vigilance) and awareness (e.g., awareness of the environment and of the self, thinking) [1]. Arousal is supported by several brainstem neuron populations that directly project to both thalamic and cortical neurons. Awareness is thought to be dependent upon the functional integrity of the cerebral cortex and its subcortical connections [2]. Several hypotheses attempt to explain the neuronal correlates of stimuli awareness: from a localizationist point of view to a synchronization of distant structures (see for example [3, 4]). Currently, consciousness cannot be measured objectively by any machine. Its estimation requires the interpretation of several clinical signs.

Coma is defined as a state of unarousable unresponsiveness in “which the subject lays with the eyes closed” and has no awareness of self and surroundings [1]. Coma can result from diffuse bihemispheric cortical or white-matter damage after neuronal or axonal injury, or from focal brainstem lesions that affect the pontomesencephalic tegmentum or paramedian thalamic bilaterally [5]. After some days to weeks comatose patients will eventually open their eyes. When this return of ‘wakefulness without awareness’ is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state (VS).

The VS may be a transition to further recovery, or not. It can be diagnosed soon after a brain injury and can be partially or totally reversible or it may progress to a persistent vegetative state or death. In the VS, the brainstem is mostly spared whereas the gray or white matter of both cerebral hemispheres is widely and severely damaged. The functional preservation of the brainstem maintains arousal and autonomic functions in these patients. The other hallmark of the VS is a systematic impairment of metabolism in the polymodal associative cortices: bilateral prefrontal regions, Broca's area, parietotemporal, and posterior

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parietal areas and precuneus (see Fig. 1 [5]). These regions are important in various functions that are necessary for consciousness, such as attention, memory, and language. In cohort studies of patients in VS, simple noxious somatosensory [6] and auditory [7, 8] stimuli have shown systematic activation of primary sensory cortices and lack of activation in higher order associative cortices from which they were functionally disconnected.

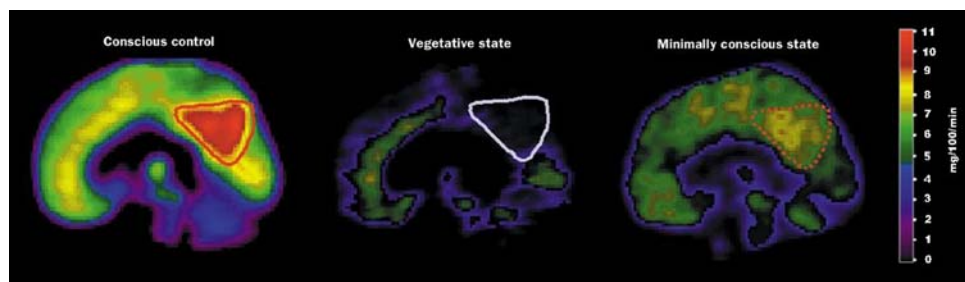
Signs of voluntary motor activity should be actively searched for in VS patients, as they herald the minimally conscious state (MCS) [9]. Functional communication indicates the next boundary—emergence from MCS—in the course of recovery. MCS describes patients who are unable to communicate, but who demonstrate inconsistent but reproducible behavioral evidence of awareness. Patients in MCS may show oriented response to noxious stimuli, sustained visual tracking, command following, intelligible verbalization, or emotional, or motor behavior that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Overall cerebral metabolism in MCS is decreased to values slightly higher but comparable to those observed in the VS (see Fig. 1). The medial parietal cortex (precuneus) and adjacent posterior cingulate cortex seem to be brain regions that differentiate patients in MCS from those in VS [5]. Interestingly, these areas are among the most active brain regions in conscious waking and are among the least active regions in altered states of consciousness such as general anesthesia, sleep, hypnotic state, dementia, and postanoxic amnesia.

Non-communicative coma survivors may show visual, motor, or verbal behaviors, which can be seen as signs of consciousness. Actually, it is very speculative to say that these behaviors are associated to some kind of consciousness. We can assert that a patient is conscious *only* when she/he communicates her/his contents of consciousness. In the absence of such reports, as it is the case in VS and MCS patients, event-related potentials (ERPs) could bring objective information on residual cerebral functioning.

ERPs objectively evaluate sensory and cognitive functions at the patient's bedside offering diagnostic and prognostic value.

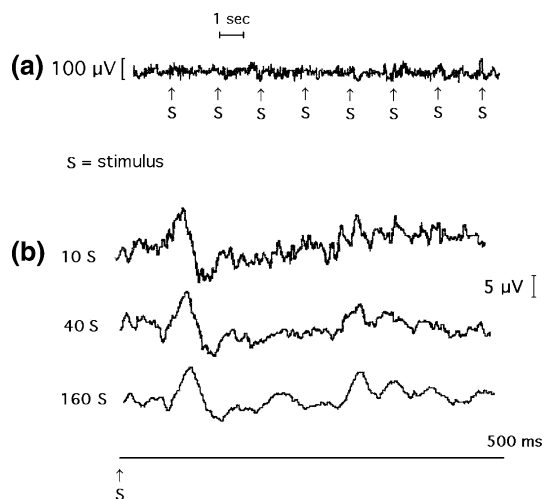
### The ERPs Technique

The ERPs method is a derivative of the electroencephalography (EEG). The EEG, allowing recording of the spontaneous electrical brain activity, permits to identify the level of vigilance and to detect functional cerebral anomalies such as seizures or encephalopathy (i.e., exploring general physiological or pathophysiological states). However, the EEG cannot quantify the small changes induced by sensory, motor, or cognitive activities because they are buried in the recorded whole brain activity. These more subtle functional variations can be explored by averaging the EEG activity, according, for example, to the onset of a repeated stimulus. By this procedure, the activity time-locked to the stimulus is revealed and the spontaneous brain activity cancels out, simply for statistical reasons (see Fig. 2). This technique, called ERPs, reveals voltage deflexions (or components or potentials) indexing the successive activation of the nervous structures implied in the studied sensory, motor, or cognitive paradigms. ERPs, obtained in response to a sensory stimulation, reflect the time course of information processing from “low-level” peripheral receptive structures to “high-order” associative cortices. Short-latency ERPs, or exogenous ERP components (ranging from 0 to 100 ms), correspond to the activation of the ascending pathways to the primary cortex. Cognitive ERPs, or endogenous ERP components (obtained after 100 ms), reflect both sub-cortical and cortical structures, including associative areas. While, short-latency ERPs are affected by the physical properties of the stimulus, cognitive ERPs depend on the psychological significance of the stimulus and are linked to the experimental condition and the level of arousal or attention.



**Fig. 1** Metabolism in healthy participants, VS and MCS patients. Sagittal images of resting cerebral metabolism in healthy participants (left part of the figure), in patients in a VS (middle part) and in

patients in minimally conscious state (right part). Mg glucose metabolized per 100 g of brain tissue per minute (adapted from Laureys et al. [5])



**Fig. 2** Event-related potentials principles. Electroencephalographic (EEG) activity is recorded by scalp electrodes and stimuli are presented several times (a). By merging epochs of EEG, according to the beginning of a stimulus, the activity time-locked to the stimulus is revealed and the spontaneous brain activity cancels. The more stimuli presented the more spontaneous brain activity cancels simply for statistical reasons (b) (adapted from Guérit et al. [10])

### Predicting Values of ERPs

Predicting functional outcome after coma is an important aspect of intensive care. Predicting values of ERPs are estimated by calculating the relationship between the presence (or the absence) of a component and the outcome of patients. Positive predictive value for favorable outcome (PV+) estimates the percentage of patients who will recover when a component is evoked (it is the number of patients with favorable outcome and with the component/total number of patients with the component). In contrast, positive predictive value for unfavorable outcome (PV−) estimates the percentage of patients who won't recover when no component is evoked (it is the number of patients with unfavorable outcome and without the component/total number of patients without the component). The relationship between ERPs and outcome could be also assessing from the outcome. Sensitivity for unfavorable outcome (or specificity for favorable outcome; Sp+) estimates the percentage of patients who had not a component when the outcome is bad (it is the number of patients with unfavorable outcome and without the component/total number of patients with unfavorable outcome). In contrast, sensitivity for favorable outcome (or specificity for unfavorable outcome; Sp−) estimates the percentage of patients who had a component when the outcome is good (it is the number of patients with favorable outcome and with the component/total number of patients with favorable outcome).

### Short-Latency ERPs

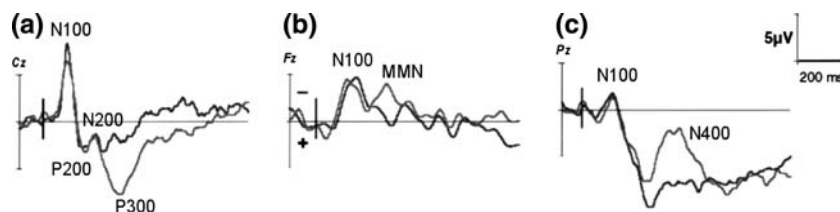
Short-latency ERPs are routinely used because they are a validated means to predict poor outcome (for a recent review, see Laureys et al. [11]). They show a very low rate of false-negative predictions, i.e., most patients bilaterally missing these potentials show a negative prediction outcome. On the other hand, the rate of false-positive predictions is high, i.e., well-preserved potentials are recorded in patients who have a bad clinical prognosis. If both somatosensory (i.e., repeated electrical stimulation of the median nerve at the wrists) and auditory stimulations (i.e., presentation of “clicks” using headphones) have been used, they bring relatively similar conclusions. Visual ERPs (using goggles with flashing LEDs) are of limited use at the intensive care setting because they fail to show systematic activation even in healthy subjects.

A recent meta-analysis confirmed that somatosensory evoked-potentials (SEPs), which reflect the activation of the subcortical somatosensory pathways and of the primary somatosensory cortex, are superior, with few exceptions, to pupillary responses, motor responses, Glasgow Coma Scale, EEG, and computed tomography for the prediction of favorable or unfavorable outcome after acute severe brain damage [12]. Bilateral absence of SEPs among patients in coma is strongly associated with a non-awakening prognosis (PV− near 100%), i.e., death or permanent VS [13–16]. At the same time, all patients with favorable outcome have developed normal SEPs (Sp− near 100%). In contrast, normal SEPs are associated to a great number of false positives (for reviews see [13, 17–19]) suggesting that SEPs are not a good predictor of recovery.

The absence of brainstem auditory-evoked potentials (BAEPs), which are evoked in the first 10 ms and reveal the activity from the auditory nerve to the inferior colliculus [20], can be seen as a reliable prognosticator for poor outcome when there is no evidence of peripheral auditory damage. On the other hand, the presence of normal BAEPs does not reliably indicate a good outcome [10, 13, 21–23]. Similarly, the absence of middle-latency auditory-evoked potentials (MLAEPs; appearing between 10 and 50 ms and probably signing the activation of thalamus and primary auditory cortex) is strongly associated with bad outcome in postanoxic coma [23–25].

### Cognitive ERPs

If short-latency ERPs are useful to predict unfavorable outcomes in coma survivors, they are less helpful in prognosticating recovery. Moreover, they only estimate the integrity of ascending pathways and not of possible residual cognitive functioning. Some recent studies suggest that the



**Fig. 3** Auditory cognitive ERPs in healthy participants. **(a)** In oddball paradigms, monotonous stimuli (gray trace) elicit the N100, P200 waves, and deviant stimuli (dark trace) elicit the N100, P200, N200, and P300 waves (note that P200 and N200 waves were not systematically investigated in patients with disorders of

consciousness). **(b)** In inattentive oddball paradigms, a MMN is evoked by the deviant stimulus (dark trace), following the N100 wave. **(c)** Incongruous words (dark trace) elicit N100 and N400 components whereas congruous words do not elicit the N400 component

use of auditory cognitive ERPs might complement short-latency ERPs evaluation at the intensive care unit. As compared to early ERPs, cognitive ERPs are very dependent on the experimental conditions. Thus, it is very important to perform clinical explorations in optimal vigilance, attention, and habituation settings. This implies to use a number of stimuli which is optimized to both dig up ERPs from the background EEG activity and to avoid habituation phenomena. Since all published studies are not conducted in similar conditions, the results are not homogenous.

We reviewed Medline from January 1, 1980 to June 1, 2007 (search terms: coma, outcome, and evoked potentials) and selected all studies investigating cognitive ERPs (N100, MMN, P300, or N400) of comatose and post-comatose (VS and MCS) patients, and in which prognostic values were described.

#### The N100 Component

The N100 wave is a negative deflection, elicited around 100 ms, in response to any auditory stimulus (see Fig. 3a–c) [26]. It corresponds to the activation of the auditory cortex (and perhaps also of dorsolateral prefrontal areas) [27–29].

If the presence of a N100 in comatose and post-comatose patients suggests that the primary auditory cortex is functionally preserved, it does not appear to be a good predictor of bad or good outcome (see Fig. 4). Some authors suggest that its presence predicts (see predictive values of N100 in Table 1) recovery [23, 34, 35] while others do not [31–33]. On the other hand, two studies suggest that its absence appears to be a good predictor of bad outcome and that, among patients who recovered, a high proportion of them had a N100 [31, 32].

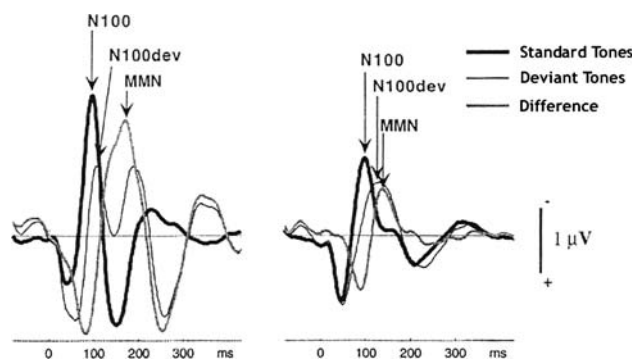
#### The Mismatch Negativity (MMN)

The MMN is a negative component elicited after 100–200 ms by any change or ‘mismatch,’ in a sequence of monotonous auditory stimuli (i.e., an ‘oddball paradigm’)

in inattentive subjects—who for example watch TV (see Fig. 3b) [41, 42]. It is relatively small in amplitude; thus it is generally displayed as a difference wave computed by subtracting the repetitive from the deviant response. For the auditory modality, the primary auditory cortex and prefrontal areas participate to its generation [43, 44]. MMN may index an automatic stage of information processing after a comparison process between the afferent input and a memory trace developed by the repetitive stimulation [45].

Data on MMN in comatose patients converge to the conclusion that it is a very good predictor of recovery (see Table 1 for predictive values of MMN), notably in anoxic coma [36, 46]. In a prospective cohort study on 346 comatose patients, Fischer et al. [23, 25, 35] reported a high prognostic value of the MMN for recovery, all etiology confounded (see Fig. 4). In both groups, a very high proportion of patients who did not recover did not evoke a MMN component but low Sp– and PV– were also observed. Similar results have been obtained, more recently, by Naccache et al. [47].

Kotchoubey et al. found a MMN in 65% of patients in VS and in 34% of patients in MCS [48, 49]. Interestingly, they showed that complex tones elicited a MMN significantly more frequently (in 50% of patients) than pure tones (24%). Very recently, a correlation has been found between



**Fig. 4** Auditory cognitive ERPs in comatose patients. N100 and MMN components are elicited both in healthy subjects (left part of the figure) and in comatose patients, with GCS  $\leq$  8 (right part) adapted from Fischer et al. [30]

**Table 1** Predictive values of cognitive ERPs (in %)

	Authors	Number of patients	PV+, rate % (95% CI)	PV-, rate % (95% CI)	Sp+, rate % (95% CI)	Sp-, rate % (95% CI)
N100	Mutschler et al. [31]	20	40 (12–73)	<b>100</b> (69–100)	63 (35–85)	<b>100</b> (40–100)
	Glass et al. [32]	8	29 (4–71)	<b>100</b> (2–100)	17 (0–64)	<b>100</b> (16–100)
	Guérit et al. [33]	103	77 (66–87)	54 (43–65)	56 (45–67)	76 (65–85)
	Mazzini et al. [34]	21	<b>83</b> (58–95)	41 (22–66)	<b>83</b> (58–95)	41 (22–66)
	Fischer et al. [35]	346	<b>80</b> (74–86)	48 (40–56)	65 (55–73)	67 (61–73)
MMN	Kane et al. [36]	54	<b>100</b> (86–100)	45 (27–64)	<b>100</b> (77–100)	56 (40–72)
	Fischer et al. [35]	346	<b>89</b> (80–94)	38 (32–44)	<b>91</b> (83–95)	33 (27–39)
P300	Yingling et al. [37]	8	<b>100</b> (16–100)	75 (35–97)	<b>100</b> (54–100)	50 (7–93)
	Gott et al. [38]	20	<b>83</b> (36–99)	71 (42–92)	<b>91</b> (59–99)	56 (21–86)
	Rappaport et al. [39]	8	<b>88</b> (47–99)	<b>100</b> (2–100)	50 (1–99)	<b>100</b> (54–100)
	DeGiorgio et al. [17]	20	<b>83</b> (36–99)	71 (42–92)	<b>91</b> (59–99)	56 (21–86)
	Mutschler et al. [31]	20	50 (12–88)	<b>93</b> (66–99)	81 (54–96)	75 (19–99)
	Guérit et al. [33]	103	<b>100</b> (96–100)	41 (30–52)	<b>100</b> (96–100)	18 (10–28)
	Signorino et al. [40]	25	<b>87</b> (60–98)	50 (19–81)	71 (29–96)	72 (47–90)
	Glass et al. [32]	8	33 (4–78)	<b>100</b> (16–100)	33 (4–77)	<b>100</b> (16–100)
	Mazzini et al. [34]	21	58 (34–78)	0 (0–16)	<b>83</b> (58–95)	0 (0–16)
	Lew et al. [14]	22	71 (29–96)	<b>87</b> (59–98)	<b>87</b> (60–98)	71 (29–96)

Positive predictive value for favorable (PV+) and unfavorable outcome (PV-), and sensitivity for unfavorable (Sp+) and favorable outcome (Sp-) are reported for articles in which these values were reported. Values in bold are superior to 80%

MMN amplitude and clinical diagnosis: Wijnen et al. showed, in 10 vegetative patients, that MMN amplitude increases with recovery to consciousness, i.e., when patients reached a MCS [50].

### The P300 Wave

The P300 response is a positive wave which is elicited, around 300 ms post-stimulus, when subjects detect a rare and unpredictable target stimulus in a regular train of standard stimuli, i.e., in the oddball paradigm (see Fig. 3a) [51]. This potential is larger when the probability of occurrence of the target stimulus decreases [52]. The P300 response is composed by two “sub-components” modulated differentially by experimental manipulations: the P3a peaks near 250 ms (and has maximal frontal topography) and the P3b peaks near 350 ms (and has maximal parietal topography) [53]. The P3a amplitude is quite similar in active or passive attentional tasks (in the second, it follows the MMN) whereas P3b is larger in active oddball tasks, suggesting that the P3a is more sensitive to involuntary detection and P3b to attentional discrimination. However, P3b is still elicited in passive paradigms [54] and its amplitude is particularly large when the deviant stimulus is salient for the subject, for instance presenting the own name as compared to other names [55, 56]. This suggests that P3b is not only dependent on the subject’s attention but

also on the importance of the stimulus for the subject. This latter property is very helpful for the investigation of non-communicating patients, as we will see in the next paragraph. The P300 can be seen as a post-decisional process since it follows the EMG response of the stimulus detection [57]. Furthermore, it would reflect the closure of the cognitive period following the identification of the stimulus [58]. Multiple intracranial generators have been postulated for the auditory P300: medial (hippocampal) and lateral sources of the temporal cortex, as well as thalamic, parietal, and prefrontal generators [59–62].

In most studies the presence of a P300 correlates with favorable outcome in comatose patients (see predictive values of P300 in Table 1). However, the data are not systematically convergent. While a great number of studies suggest, as MMN data, that among patients who developed a P300 wave a high proportion of them recovered [17, 33, 37, 38], others do not [31, 63]. This variability could be explained by the limited number of patients studied, as well as the limited number of patients evoking a P3 response to deviant tones.

The use of emotional stimuli increases the percentage of traumatic comatose patients exhibiting P300 activity, and helps to investigate more ecological functions. Signorino et al. used both a conventional oddball paradigm and an oddball paradigm in which the tones were coupled to emotional verbal stimuli (i.e., a short phrase spoken by a member of the family or the patient’s name) and obtained a

P300 in 36–38% of comatose patients in the first condition and in 52–56% in the second condition [40, 64]. In their studies, a high proportion of patients evoking a P300 recovered. Lew et al. confirmed that an emotional stimuli (presenting “mommy”) evoke larger P300 than tones [14, 65]. They confirmed that the presence of the P300 component is more associated to good outcome than SEPs, but also that its absence is associated with a bad outcome (for Glasgow Outcome Scale between 1 and 4).

For post-comatose patients, two studies report a few number of patients evoking a P300 wave in response to deviant tones, and suggest that P300 is a very good indicator for poor outcome [32, 39]. However, these results have to be interpreted very carefully since only a small cohort of patients was investigated.

The chance to observe a cerebral response in VS and MCS patients could be increased by the use of more ecological or salient stimuli. Kotchoubey et al. showed that P300 is elicited more often in response to complex tones (i.e., more harmonic sounds) than to simple tones (in respectively 22% vs. 15% in VS and in 31% vs. 8% in MCS) [66, 67]. Emotional stimuli, such as the patient’s own name, also increase the number of reactive patients [34, 68–70]. We have previously shown that the P300 component can be observed in response to the patient’s name in MCS and VS patients, the latter failing to subsequently recover [71] (see Fig. 5). These results suggest that partially preserved verbal processing could be observed in non-communicative brain damaged patients, notably for the detection of very salient stimuli, such as the subject’s own name (this function appearing delayed in MCS and in VS patients).

### The N400 Potential

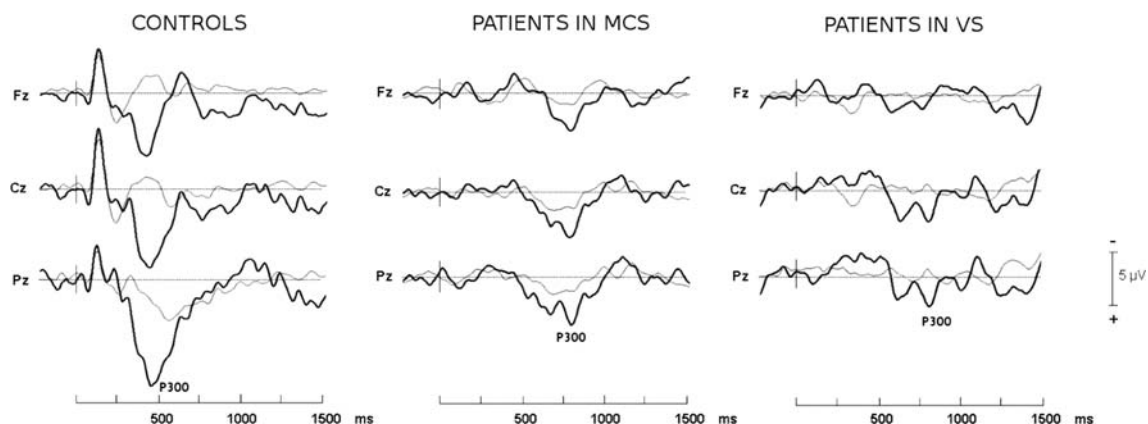
The N400 is a negative potential, occurring around 400 ms, which is larger in response to verbal stimuli that are

discordant (phonologically or semantically) with respect to a preceding verbal stimulus or sentence, than that evoked by concordant verbal stimuli (see Fig. 3c) [72]. It is possible to observe the occurrence of the N400 when subjects have to direct their attention away from the semantic aspect of the stimulus [73–75], suggesting that it reflects in part automatic processes. Medial and lateral temporal cortex, as well as the left frontal and parietal cortex, seem to participate to its generation [62, 76, 77].

Schoenle and Witzke [78] recorded ERPs in response to sentences ending with semantically congruent and incongruent words in post-comatose patients. A N400 response to incongruous words was reported in some VS patients (12%) and in a majority (77%) of ‘near-VS’ patients (the authors used this term for patients with signs of habituation, orienting reactions, or visual fixation or pursuit), and in nearly all (90%) of the patients who are not in a VS (showing ‘some meaningful behavior,’ i.e., probably in MCS). This confirms that semantic processes are relatively preserved in a majority of MCS patients but probably not preserved in a great number of VS patients. Unfortunately, these authors did not report its prognostic value.

### Conclusions

This review shows that cognitive ERPs are of interest in the clinical investigation of comatose and post-comatose states. While early ERPs (such as SEPs) are very good prognosticators of bad outcome, cognitive ERPs appear to be good predictors of favorable outcome (notably MMN and P300). Moreover, cognitive ERPs are very helpful to estimate the residual cognitive functions of comatose and post-comatose patients. They suggest the integrity of echoic memory (MMN), of acoustical and semantic discrimination (P300), or incongruent language detection (N400) in some of them.



**Fig. 5** ERPs to patient’s name. ERPs to the subject’s own name (dark trace) and to other first names (gray trace) in control subjects, in patients in a minimally conscious state and those in a vegetative state

They also show that stimuli which are more ecologic or have an emotional content increase the chance to record a cerebral response as compared to classical neutral tones.

It should be noted that results among cognitive ERP studies were heterogeneous. This could be explained in part by differences in technique, level of consciousness and muscle artifacts when tested, small numbers of patients, and varying patients' etiologies (anoxic-ischemic vs. traumatic etiology). In our view, it is not yet warranted to conclude on the true prognostic value of cognitive ERPs in neurocritical care. Before firm conclusions can be drawn, it is necessary to obtain data on large homogenous populations, to use robust recording conditions, and to more systematically investigate differences between anoxic-ischemic vs. traumatic brain damage. This would help to make a clear classification between etiology, cognitive ERPs, and outcome.

Accurate patients' classification and better prognostic indications would also be obtained by longitudinal studies (i.e., by the systematic investigation of all cognitive ERPs in one patient). This would be helpful to investigate, for example, the temporal dynamics of each ERP wave in comatose and post-comatose states. For example, it can be hypothesized that in coma survivors MMN components would appear first, followed by P300 and next followed by N400 waves, appearing first for words and later for sentences. It is likely that patients with a similar diagnosis would not all be able to evoke the same number of ERP components. Longitudinal investigations could identify predictors of good functional outcome, i.e., whether recovery from coma will be limited to a MCS (e.g., if a P300 wave is observed) or to full consciousness (e.g., if a N400 wave for sentences is observed). Currently, validated reliable and easily available makers of good functional outcome in coma are awaited to further improve the management of patients surviving severe brain damage.

At last, when cognitive ERPs method will become a routinely used tool in intensive care unit, it will be very important to combine ERPs technique with functional neuroimaging to delineate both electrophysiological and anatomical basis of recovery in brain injury.

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