Event-Related Potentials in Disorders of Consciousness

9

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Contents

Abstract

Event-related potential (ERP) is a useful method for assessment of covert cognitive functions in patients with severe disorders of consciousness (DoC). Having a poorer spatial resolution than fMRI, ERP possesses a high level of functional specificity and an excellent temporal resolution. ERP can be combined with different kinds of passive (pure stimulation) and active (instruction) tasks, which allow the investigator to check different cognitive abilities of the patients. ERP is a cheap, mobile, well-tested method; all recordings can be carried out immediately at a patient's bedside. A very broad number of cognitive processes can be tested; however, these processes are not necessarily related to consciousness. Although instruction tasks directly testing conscious awareness have also been used in combination with ERP, it remains unclear whether ERP has any advantages as compared to fMRI, the analysis of EEG oscillations, or even electromyography. Several middle-sized studies indicate that ERP can provide reliable predictors of the outcome of DoC; however, the results of these studies are inconsistent as concerns the exact role of ERP components as outcome predictors. This may be only addressed through large, multicenter longitudinal studies.

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9.1 Introduction

Evoked potential (EP) and event-related potential (ERP) are components of the EEG, time and phase locked to particular events, such as an external or an internal stimulus (e.g., the moment of muscle contraction). EP and ERP reflect, therefore, changes in the activity of neuronal populations strongly related to a specific event.

Despite conceptual similarity, the terms EP and ERP are not synonymous. The notion "evoked" presumes a strong causal relation between a stimulus and a response. This strong relation is assumed for early deflections of stimulus-related responses. These early deflections are also called "exogenous," meaning that their features are functions of the basic physical stimulus features: sensory modality, intensity, figure/background relation, etc. In contrast, later deflections of stimulus-related responses and other kinds of ERP are not "evoked" but "elicited," meaning that the corresponding events cannot be regarded as direct *causes* of these deflections. The components are also designated as "endogenous" because their features are supposed to depend not on stimulus features but rather on psychological characteristics of participants and their actual task. The borderline between "EP" and "ERP," as well as that between "exo-" and "endogenous" deflections, is not exactly defined. Most frequently, stimulus-related components with latencies up to 100 ms (after stimulus onset) are regarded as exogenous, components with latencies >200 ms as endogenous, and both terms may be applied to components between 100 and 200 ms (Picton and Hillyard 1988). From a functional point of view, it is important, however, that typical exogenous EP components reflect the propagation of stimulus-related excitation to the cortex, while later components manifest the processing of stimulus information in the cortex. Therefore, disturbances of the former indicate *sensory* disorders and the disturbances of the latter, *cognitive* disorders.

The basic methodology of EEG and ERP, the role of EP and ERP in the diagnosis and prognosis of acute disorders of consciousness (DoC), and the overview of other (non-stimulus locked) EEG oscillations are discussed in the other sections of this book (see in particular Chaps. 2, 5, 6, and 7). The present chapter is devoted to ERP in chronic DoC, in relation to their state of (disturbed) consciousness. I shall not discuss early (exogenous) EP, because these components, so important in acute coma (see Chap. 6), are not very informative in chronic conditions. It should be taken in mind, however, that exogenous EPs are prerequisites for using endogenous ERP in DoC. If the former are absent or severely disturbed, indicating disturbance of elementary sensory functions, the use of the latter for assessment of higher cognitive functions is impossible.

9.2 Functional Meaning of ERP Components

ERPs were largely investigated in reaction time (RT) experiments, in which participants receive instructions to respond (mostly manually) to particular stimuli according to particular task rules. In these experiments ERP can be regarded as a sequence of electrical deflections that happen between a stimulus and a response. This representation led to the idea that each component is a manifestation of a member in the processing chain leading from stimulus to response. This essentially behavioristic idea has subsequently been criticized on the basis of numerous findings demonstrating profound biophysical and neurophysiological similarities between ERP components having different positions in the putative processing chain, between ERP components to very different kinds of stimuli, and even between ERP components that precede particular events and those that follow these events (e.g., Kotchoubey 2006). Nevertheless, the very concept that different ERP components "manifest," i.e., make accessible, some aspects of otherwise covert cognitive operations remains valid. In the following, I shall summarize the present knowledge about the functional meaning of components, leaving aside the views still discussed.

N1 and P2 are still relatively exogenous and modality-specific components reflecting earlier and rather automatic stages of cortical processing.

Their latency and scalp location are modality dependent; e.g., the visual N1 can be up to 50 ms later than the auditory N1. The electrical sources of the N1 component are localized in the corresponding sensory areas.

The mismatch negativity (MMN) is recorded when the current stimulus deviates from the sensory model built by the brain on the basis of the preceding stimuli (Näätänen and Winkler 1999). Although some authors claim the existence of an MMN in different sensory modalities (e.g., Gayle et al. 2012), presently only *auditory* MMN has been tested in clinical practice. The standard paradigm to elicit an MMN is the so-called oddball paradigm, in which frequent and rare (“oddball”) tones are randomly presented (see also Chap. 7). The former elicit N1 and P2 and the latter, in addition, the MMN. The frequency of rare tones is about 0.1 or even less. Since at least 150 rare tones are recommended (Duncan et al. 2009), the whole sequence includes at least 1,500 stimuli. The latency of the MMN is about 200–250 ms; therefore two or three stimuli per second can be presented, making together 8–10 min. The MMN has two main sources, in the temporal and frontal lobes. The largest negativity is usually recorded at Fz and the largest positive amplitudes in the same time window, at mastoid electrodes. This means that, in order to record an MMN, one should not use mastoid electrodes as reference.

In this typical paradigm, rare tones (also called deviants) deviate from the frequent tones (standards) by one feature, e.g., pitch or duration. The MMN also responds to very complex features such as a fine change in the spectrum of the tone or even repetition instead of the expected alternation (Tervaniemi et al. 1994). The presence of an MMN indicates the ability of the brain’s sensory system to analyze the corresponding feature but tells nothing about other characteristics. Therefore, a multifeature paradigm has been proposed, in which up to five different capacities of auditory discrimination are tested at once (Näätänen et al. 2004). An example of such a paradigm is presented in Fig. 9.1. Each deviant differs from standards by only one feature and remains identical to the standards regarding all other features.

Like N1 and P2, the MMN is largely independent on attention (e.g., Näätänen and Alho 1995) and the functional condition of patients (Kotchoubey et al. 2003a). In particular, it is better expressed when subjects’ attention is directed away from the auditory stimuli, and the subjects perform a different (e.g., visual) task. The MMN to attended stimuli is not suppressed, but it is overlaid with other ERP components such as N2b, which is strongly attention dependent (Näätänen et al. 2007).

The oddball paradigm is also used to elicit the component P3, or P300. This is a large positive deflection with a centro-parietal maximum and a latency between 300 and 400 ms (which may be delayed in brain-damaged patients). In contrast to the MMN, P3 is best pronounced in response to attended deviants; it is maximal when the eliciting stimuli are targets in a task (e.g., they should be counted) and smaller in a no-task condition (“just listen to stimuli”) and can even disappear when the attention is deployed to other stimuli. The putative neural basis of P3 is a complex network including temporal and parietal cortical areas and subcortical centers such as the hippocampus. Therefore, while the MMN reflects a low-level, relatively passive sensory discrimination, P3 manifests higher-level, complex discrimination processes in which a stimulus is selected as a target.

The large amplitude of P3 permits to limit an oddball sequence to 200–300 stimuli. Bostanov and Kotchoubey (2006) obtained reliable P300 after only 9 deviants in a passive (just-listen) condition. Usually, however, 20–30 deviants should be averaged. On the other hand, the development of P3 requires more time than that of the MMN, and thus interstimulus intervals of at least 0.9–1 s are necessary (Duncan et al. 2009).

The difference between the MMN, N2b, and P3 is well illustrated in a dichotic listening paradigm, in which two stimulus trains are presented in parallel in two ears. The task is to count rare deviants in one ear, ignoring all stimuli in the other ear. The MMN is well pronounced in response to deviants in the ignored ear. N2b can be recorded to all stimuli in the attended ear, although its amplitude may be

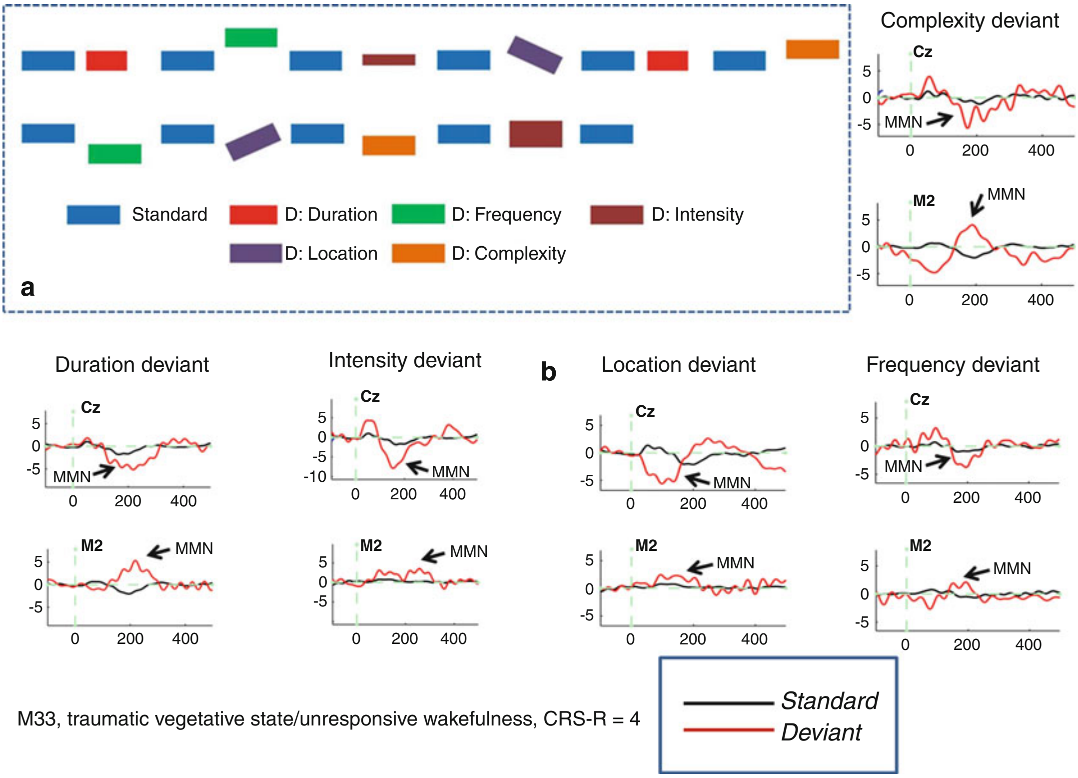

Fig. 9.1 (**a**) Schema of a multifeature MMN paradigm. The standard stimulus randomly alternates with one of the five deviants, each of which differs from the standard by one feature only being identical to the standard in respect to all other features (e.g., a complexity deviant has the same perceived pitch, loudness, duration, and location as the standards). (**b**) A vegetative-state/unresponsive wakefulnes patient who exhibited significant MMN responses to all five kinds of deviation. Negativity is plotted downwards. Note the large negative deflections around 200 ms post stimulus at Cz and simultaneous positive deflections at mastoids (M2). *CRS-R* Coma Remission Scale-Revised, full score

larger to deviants than to standards. A typical P3 is elicited only by target stimuli, i.e., by deviants in the attended ear.

The N400 is a specific ERP component elicited by violations of a meaningful context. A typical N400 paradigm includes sentences with a meaningless (semantically incongruent) final word, such as "The waiter served coffee with milk and shoes." Compared with a corresponding congruent ending (…"sugar"), the word "shoes" results in a large negative centro-parietal deflection with a peak latency of about 400 ms. The same effect can also be elicited by incongruent word pairs (*cat-moon*, compared with *cat-mouse*), semantic violations in a row of words (*tiger, wolf, bear, polecat, stomach*), or even by nonverbal stimuli such as a picture that violates the context of other pictures.

From the point of view of DoC, it is important to note that an N400 to semantic violations indicates a high-level processing of meaningful stimuli but does not prove *conscious* verbal comprehension. Congruent verbal expressions frequently contain strongly associated words. In the example above, the association between *coffee* and *sugar* is stronger than that between *coffee* and *shoes*. This different association strength can result in the node *sugar* being automatically (nonconsciously) activated by the node *coffee*. According to one of the suggested models, N400 amplitude is inversely related to the preceding activation of the corresponding node (Kiefer 2002; Silva-Pereyra et al. 1999). Therefore, when the end word *sugar* is presented, it elicits a smaller N400 than previously inactive *shoes*. If this model is correct, the differential N400 effect can emerge by means of a purely automatic activation process without participation of consciousness.

In addition to these stimulus-related ERP components, two response-related components should be mentioned: readiness potential (RP, also known as “Bereitschaftspotential”) and contingent negative variation (CNV). The RP (Kornhuber and Deecke 1965) is a slowly rising negative deflection preceding voluntary movements: with a fronto-central maximum, it starts about 0.6–2 s before movement onset. Its main, symmetrical portion manifests the activity of the premotor cortex, particularly the supplementary motor area, which implies a nonspecific preparation to motor activity in general but not to a particular movement. Only the last portion of the RP (about 200 ms) includes strong participation of the primary motor cortex. When the voluntary movements are performed with hands (which is the case in most experiments), this involvement of the motor cortex is reflected in the RP having a larger amplitude on the contralateral side. This lateralized portion of the RP can also be recorded before signaled movements and not only before voluntary movements. An “inverted lateralization” (i.e., a larger negativity on the ipsilateral side) indicates covert preparations of the wrong response channel (Coles 1989).

The CNV is a predominantly frontal negative wave that appears between two strongly contingent events, most typically between two stimuli separated by a constant interval. In the standard paradigm (Walter et al. 1964), the second stimulus was a signal to a motor response, and the first stimulus had a warning function. Although this arrangement results in a large CNV, the same effect can be obtained when the first stimulus initiates a response, and the second one bears the information whether this response was correct or wrong. The CNV can also be recorded between the onset and offset of a stimulus having a sufficient and constant duration, even if no motor response is required (Bostanov et al. 2013). When the interval separating the two events is sufficiently long (3–4 s), one can see that the negative wave has two components. The early CNV manifests late stages of the processing of the first event, whereas the larger late CNV is related to the preparation to the second event.

9.3 The Problem of Individual Assessment

The ERP paradigms used in DoC patients were developed in experiments with healthy participants on the basis of a group analysis. In such experiments, the presence of an ERP component is determined after grand averaging of the waveforms of the whole group. The optimal time window for each component is defined by visual inspection of such a grand average waveform (e.g., 300–500 ms for the N400). The amplitude and latency of the component are then measured in this window, and the results are compared between groups or conditions.

This approach is not appropriate for the assessment of individual patients for the following reasons. Due to a severe brain damage, the relevant time window can be delayed and vary among patients. A component can be reliably present in a minority of patients but absent in most of them. As a consequence, the grand average across a DoC sample may not be representative for single patients. If, however, the time window is selected on the basis of patients’ individual averages (rather than the grand average), a strong bias toward false-positive findings can follow. It is intuitively clear that, having unrestricted freedom of individual adjustment, we could find “significant” differences between almost any two waveforms. Finding the middle way between the Scylla of underadjustment (leading to information loss and false-negatives) and the Charybdis of overadjustment (leading to false-positives) remains a matter of art rather than science. The situation is even worse if ERP components are quantified by means of subjective assessment (Valdes-Sosa et al. 1987). Unfortunately, this method is still used by many research groups applying ERP in neurological patients. If the experts are aware of the clinical and demographic characteristics of the patient (which is often the case), their assessment can be biased by this knowledge.

Several methods have been suggested to solve this problem. From a statistical point of view, they vary in respect of power and statistical strength, and from the computational point of view, the difference is important between the permutation-based techniques and those not using permutation. A simple and useful non-permutational technique was proposed by Guthrie and Buchwald (1991). A running *t*-test is calculated at each consecutive time point across an interval that can be defined broadly enough to rule out subjectivity factors. Further, the covariation between adjusted points is estimated. This covariation determines the minimum length of the row of significant *t*-values necessary for identification of a significant ERP effect. Also correction by means of false discovery rate (FDR: Benjamini and Hochberg 1995) is only slightly more effortful than G&B. The method is broadly used in other domains of neurophysiology (e.g., fMRI studies) but has, to my knowledge, not been applied for ERP assessment of neurological patients. FDR, however, is prone to underestimation of the covariations between different time points and electrodes (Groppe et al. 2011a), and its results depend on the real presence or absence of an effect, i.e., on the number of false null hypotheses (Groppe et al. 2011b). Furthermore, some simulation experiments using FDR yielded a great variation in the number of false-positive findings (Korn et al. 2004), although more realistic simulations did not replicate these results (Groppe et al. 2011b).

Using permutation to correct for false-positives in ERP research and evaluation was suggested by Blair and Karninski (1993) and later on employed in the analysis of both ERP (e.g., Lage-Castellanos et al. 2008) and rhythmic EEG components (e.g., Laaksonen et al. 2008). The simple underlying idea is that if there is no difference between the conditions (e.g., “rare” versus “frequent”), then it does not matter which particular trial belongs to which condition. The result would be the same if we deliberately swap trials between conditions, except purely random variations. If we repeat this procedure, say, 10,000 times, we can see how often the resulted statistics (e.g., a *t*-test) will attain or even exceed the corresponding statistics obtained when the trials are correctly assigned to the conditions. The great advantage of permutation tests is that they are exact; this means that they do not result in statistical estimates of (or approximations to) some critical value but, rather, in this critical value itself. They are distribution-free and do not require any assumptions except that observations across subjects are mutually independent. The disadvantage is rather high computational demands. This is particularly true if permutation is carried out for each single data point as originally suggested. Then, having a rather moderate data set with 300 time points, 30 electrode channels, and 2,000 permutations (a minimum!), 18 million *t*-tests (or other similar statistics) have to be computed for one analysis.

To reduce this effort, one can group together the statistics obtained at adjacent time points and electrodes, resulting in a clustered data (Maris and Oostenveld 2007). Usually, statistics that do not reach a threshold level (e.g., at least two adjacent *t*-tests reaching an uncorrected *p*-value of 0.05) are filtered out before clustering. The resulting relatively small number of variables then undergoes a permutational analysis (Oostenveld et al. 2011; Groppe et al. 2011a). This method is implemented in MATLAB and used in several ERP studies. However, a problem of this procedure is the presence of several clustering parameters (the primary significance threshold, the definition of neighborhood, etc.) that are open for arbitrary decision and whose choice can strongly affect the results. When the most general question is asked, i.e., whether two responses of a patient differ or not, clustered permutation techniques appear to be superior to FDR and non-clustered permutation tests (Groppe et al. 2011b). However, the stronger the need to localize the difference and to ascribe it to a particular ERP effect, the more problematic is the use of the clustering method, because local events can be smeared by informal clusterization.

The technique of *t*-CWT (studentized continuous wavelet transformation: Bostanov 2003; Bostanov and Kotchoubey 2006) was introduced with the explicit aim of extraction of the maximum information contained in the difference

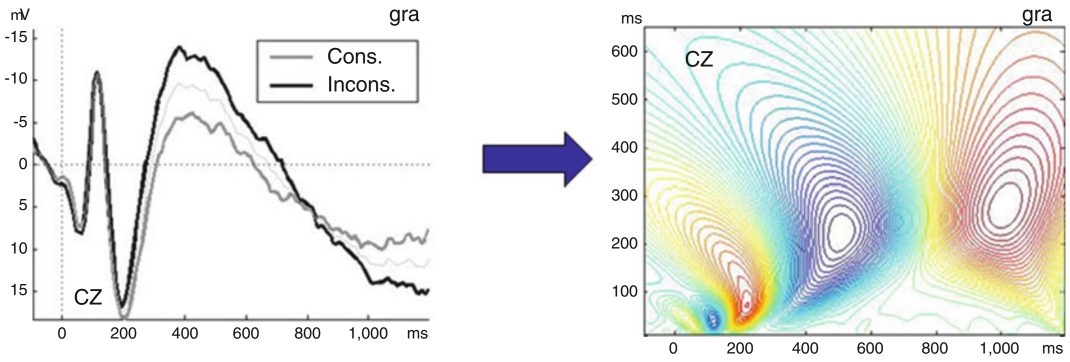

Fig. 9.2 *t*-CWT transformation allows us to transform a two-dimensional ERP (amplitude/time) into a three-dimensional pattern (amplitude/scale/time). *Left panel*: a typical ERP at Cz in a verbal paradigm with semantically consistent (*gray line*) and inconsistent (*black line*) words; the latter elicit an N400. Negativity is plotted upwards. *Right panel*: the same ERP after *t*-CWT transformation. The ordinate shows scale values (scale =1/frequency), while the amplitudes are shown in a color scale from *red* (positive) to *blue* (negative)

between two waveforms corresponding to the two conditions in a typical ERP experiment. In contrast to the univariate methods depicted above, *t*-CWT is a technique of a multivariate analysis that takes into account all covariations between spatial and temporal points. Studentization (i.e., the representation of the difference between two ERP waveforms or between one waveform and zero, in *t*-scores) allows the investigators to attain the optimal power possible with a given signal/noise ratio. The target ERP components can be identified and localized by means of a continuous wavelet transformation, which allows to represent the response as a three-dimensional figure with the axes time, scale (=1/frequency), and size (amplitude). Therefore, the windows for the components are defined in a fully objective manner (Fig. 9.2). It should be said that the main achievements of this method have their costs: the backside of the independence of covariations is the use of a parametric Hotelling test, whose assumptions (e.g., normal distribution) are not always fulfilled, and the optimization of information extraction has the disadvantage that the alpha inflation is not controlled but, in contrast, maximized. However, both problems are removed when the final set of data, again, undergoes a permutation test with at least a few thousand permutations. This test results in an unbiased, powerful, and distribution-free estimate of an ERP effect.

Although the *t*-CWT method is theoretically optimal, this does not mean that its additive value in the diagnostic use is practically significant as compared with simpler, less effortful procedures. Even if the method is much more powerful than the classical area analysis and several multivariate techniques such as the discrete wavelet transform (Bostanov and Kotchoubey 2006), it has not been directly compared with FDR and clustered permutation tests. Recent studies with both simulated (Real et al. 2014) and real DoC patients' data showed that *t-CWT* is significantly more sensitive than G&B procedure (as theoretically expected) but that the difference is not very large and partially compensated by speed and easiness of the running *t*-test. More data are necessary to give precise recommendations about using different quantitative methods of individual assessment of DoC subjects.

9.4 ERP Manifest Remaining Cognitive Processes in DoC Patients

About 20 years ago, several publications (Reuter et al. 1989; Marosi et al. 1993; Moriya et al. 1995) reported P3 findings in some patients diagnosed as vegetative/unresponsive wakefulness (VS/UWS). These early reports, however, were sporadic and clinically unreliable. Thus Marosi et al. (1993) claimed to find "P3 in the vegetative state," although only two of the reported 23 patients apparently corresponded to the modern diagnostic criteria of VS, and no P3 was recorded in these patients. The first larger study was carried out by Schoenle and Witzke (2004) (preliminary data reported 8 years earlier: Witzke and Schönle 1996). They examined 43 VS/UWS patients and 23 patients "near vegetative state," who might roughly have fulfilled the criteria of the minimally conscious state (MCS). The N400 paradigm with semantically congruent and incongruent sentence endings was used. An N400 to semantic incongruence was found in 5 VS/UWS and 17 "near VS" patients. Among 54 severely brain-damaged but conscious patients, the N400 was obtained in 49 cases. This was probably the first indication that even "definitive VS" patients possess so-called higher cortical abilities, in this case the ability to semantic word categorization. Unfortunately, the method of N400 quantification was very subjective, and the raters might have known the diagnoses of patients.

Kotchoubey et al. (2005) applied a quantitative assessment of ERP components, in which the only subjective factor remained the definition of individual component time window. The integral amplitude was automatically measured in this window in each single trial and then statistically compared between conditions (e.g., standards versus deviants in the oddball paradigm; semantically congruent versus incongruent words in semantic paradigms). These authors reported even higher than (Schoenle and Witzke 2004) rates of N400 in both VS/UWS and MCS patients. This finding has recently been confirmed by Balconi et al. (2013) and Steppacher et al. (2013) using objective ERP evaluation techniques; the latter study included a sample of as many as 175 DoC patients.

As regard P3, it could be obtained in 20–25 % of DoC patients (Witzke and Schönle 1996; Kotchoubey et al. 2001, 2005; Cavinato et al. 2009 [only traumatic VS/UWS patients], Schnakers et al. 2008 [P3 found only in MCS but not in VS/UWS], Fischer et al. 2010; Müller-Putz et al. 2012; Guger et al. 2013; Steppacher et al. 2013). This may indicate activation of complex cortico-subcortical networks in response to target stimuli in many patients. Unfortunately, large brain damage of some patients makes it sometimes difficult to distinguish between the "real" P3 (also called P3b) from the so-called novelty P3 (or P3a), reflecting more superficial orienting response to novel stimuli (Kotchoubey 2005; Fischer et al. 2010).

More conservative approaches may result, however, in substantially lower rates of P3. Faugeras et al. (2012) used a design in which P3, if recorded, could necessarily be the P3b; they obtained this component only in 7 of 13 conscious patients, 4 of 28 MCS, and 2 of 24 VS/UWS, while these two also changed to MCS in a few days after examination. Chennu et al. (2013) used a system of 91 electrodes to separate P3a from P3b and found a P3a in 1 of 9 VS/UWS and 3 of 12 MCS patients. These poor results are particularly surprising because this study was one of a very few in which both ERP and fMRI measures of cognition in DoC patients, and the fMRI experiment (Owen et al. 2006) revealed the ability to follow instruction in 4 VS/UWS and 5 MCS patients. Therefore, the high-level ability to understand and consistently follow verbal commands was found with a rate more than twice as high as the low-level involuntary orienting reaction manifested in the P3a.

The MMN is already used in acute coma as a standard EEG measure (e.g., Fischer et al. 1999, 2010) (see also Chap. 7). The component was also found in some one-third of VS/UWS and MCS patients (Kotchoubey et al. 2005; Wijnen et al. 2007; Fischer et al. 2010; Luauté et al. 2010; Faugeras et al. 2011, 2012; Risetti et al. 2013), indicating these patients' ability to sensory discrimination. Recent experiments using the multifeature MMN paradigm (Guger et al. 2013) indicate that this ability can be retained in an even larger number of patients than that identified with a unifeature paradigm (see Fig. 9.1 above). Significant differences between VS/UWS and MCS were reported only by Boly et al. (2011) in a study with 13 MCS and 8 VS/UWS patients, in which the ERP data underwent a source analysis with a following dynamic causal modeling (DCM) analysis. The data were interpreted as suggesting that top-down connections from the frontal cortex to primary auditory areas, presented in both healthy individuals and MCS patients, were lacking in VS/UWS, while bottom-up connections from the auditory to the frontal cortex remained preserved in all patients. However, the lack of any sign of an MMN in the primary data of VS/UWS patients and the dramatic differences between these data and those of all other MMN studies strongly question the use of complex mathematical techniques such as DCM (King et al. 2011). Most probably, both feedforward and feedback connections were broken in this small sample of VS/UWS patients (King et al. 2011). Only one study (Faugeras et al. 2011) investigated the CNV preceding the last stimulus in the sequence and probably reflecting anticipation of this stimulus; this wave was obtained in 12 of 28 MCS patients, 9 of 24 VS/UWS patients, and 8 of 13 conscious patients.

What about a presumable hierarchy of these components? As stated above, the lack of early subcortical EP components precludes the emergence of later, cortical ERP components. On the other hand, almost all patients having at least partially preserved brain stem auditory EP also exhibit cortical exogenous components P1, N1, and P2 or at least some of these three. Within the cortical components, however, no strict rule like "if X is absent, Y must be absent too" can be established. Recent studies (Guger et al. 2013) demonstrated that there is no earlier ERP effect whose loss completely rules out a later effect; thus there can be an MMN without N1, P3 without N1 and MMN, etc. (see also Kotchoubey et al. 2005). This means that an ERP test battery applied for DoC patients should always check *all* important cognitive components and that the examiners should not stop when initial findings are negative.

As regards *emotional* stimuli, Bostanov and Kotchoubey (2004) recorded a component N300 in response to affective exclamations. The wave is, most probably, an early variety of the N400 related to violations of emotional – instead of semantic – context. Later on, the N300 was also found in VS/UWS and MCS patients with mostly left hemispheric lesions (Kotchoubey et al. 2009). In the same study, a magnetoencephalographic analysis of the N300 showed, however, that it cannot be attributed to emotional processing directly but, rather, to a later cognitive process of detection of affective mismatch.

Another kind of *affective*, highly meaningful stimuli is a subject's own name (SON) that in healthy individuals elicits P3 of larger amplitude as compared with other similar stimuli (Berlad and Pratt 1995). Kotchoubey et al. (2004) applied this stimulus in a group of VS/UWS patients and did not find a significant amplitude differences between SON and another stimulus of the same frequency in any of them. A single MCS patient developed a paradoxical response in form of a slow frontal negativity instead of a parietal P3. No SON response in VS/UWS was also found in a later study (Schnakers et al. 2008); however, these authors found a clear P3 increase to SON in MCS. Qin et al. (2008) investigated a mixed group of acute and chronic DoC patients: 7 of 12 patients exhibited a significant increase of the MMN (rather than P3) to SON. Two studies led to more positive results. One of them yielded both MMN and P3 effects to SON (in the passive condition) in almost every patient: 7/8 VS/UWS and 3/3 MCS (Risetti et al. 2013). In the other study, a P3 increase to SON was found in 3/5 VS/UWS and 6/6 MCS patients, although the response was considerably delayed in VS/UWS as compared with MCS; in addition, the authors examined four patients with locked-in syndrome (LIS) and also obtained the effect in each of them (Perrin et al. 2006). The design of the last study was different from a typical oddball, as a patient's own name was presented among other, unrelated names.

SON data illustrate one more important point in using ERP in DoC: stimuli that are most efficient in eliciting a response must possess sufficient complexity. The own name is a much more complex stimulus than simple tones, and it elicits more reliable responses. Likewise, Jones et al. (2000) obtained significant MMN in VS/UWS patients to such complex auditory pattern deviation as a transition from oboe to clarinet. Both P3 and MMN in DoC are significantly more frequent and have significantly larger amplitudes when elicited by changes in harmonic tones than by acoustically equivalent changes in sine tones (Kotchoubey et al. 2001, 2003a).

ERPs have also been used to study learning in DoC. The simplest learning process of cortical habituation appears to be preserved in VS/UWS: the component N1 decreased after ten repetitions of the same tone and recovered to a tone of different pitch in a group of 33 patients (Kotchoubey et al. 2006). In contrast, Faugeras et al (2012) studied a higher-level process of ERP changes in the course of pattern stimulation. Learning effects similar to those in healthy controls were observed in one VS/UWS patient of 24 and 2 MCS patients out of 28.

9.5 ERP and Consciousness

The preceding section summarizes ERP evidence that the brain of many DoC patients is able to various kinds of stimulus processing, involving distributed cortico-subcortical networks and even the processing of word meaning. The number of VS/UWS and MCS patients who exhibit such abilities is too large to be explained by occasional diagnostic errors. However, the main diagnostic criteria of DoC include the severe disorder (MCS) or the lack (VS/UWS) of *consciousness*, not of *information processing*. This is not the same: even very complex processing operations in the brain can be done without participation of conscious awareness (van Gaal and Lamme 2012). This is equally true for the passive brain responses to the own name, which persists in coma (Fischer et al. 2008) and stage II sleep (Perrin et al. 1999). A warning should be expressed against the confusion between consciousness and attention: the fact that P3 is highly sensitive to attentional manipulations does not prove that the presence of a P3 indicates conscious perception of stimuli (Daltrozzo et al. 2012). A demonstration of preserved information processing abilities is not a proof of conscious awareness (Celesia 2013).

After a breakthrough study of Owen et al. (2006), it became clear that neurophysiological techniques can not only help to clarify the functional condition of patients' brain but also directly demonstrate *consciousness* in presumably unconscious patients. To use the ERP technique for this purpose, active paradigms should be applied, in which patients are instructed to perform a task, and the ERP data should permit the examiner to judge (in the absence of behavioral responses) whether the patient could understand the instruction. A most direct proof of consciousness can be obtained if an instruction (e.g., to move the right or left hand) is given and if ERPs demonstrate that the patient undertakes attempts to follow this instruction. To date, such a proof has been provided in patients with total locked-in syndrome (Kotchoubey et al. 2003b; Schnakers et al. 2009) but not in DoC. Another active paradigm exploits the response to a patient's own name described above. Schnakers et al. (2008) asked 8 VS/UWS and 14 MCS patients to count their own name presented as a target deviant in an oddball paradigm. The P3 amplitude to SON in the MCS group was not only significantly larger than to other stimuli but also significantly larger in the counting condition than during passive presentation of the same stimuli. No ERP response in any condition was recorded in the VS/UWS group. At the individual level, P3 amplitude increment in the counting condition was found in four MCS patients but in none of the VS/UWS subjects. A similar result was obtained when the target stimulus was a name unfamiliar to the patient. Also Risetti et al. (2013) found an effect of counting instruction to the SON response only in MCS but not in VS/UWS patients. These results indicate, first, that at least some MCS patients are able to intentionally follow instructions and, second, that the instruction is efficient in these patients, independently of the nature of stimulus; the patient's own name can be replaced with another stimulus of comparable complexity (Fig. 9.3).

Other stimuli only rarely resulted in a significant ERP response according to instruction. Chennu et al. (2013) found this response to the to-be-counted word in 1 VS/UWS patient but in none of 12 MCS patients. Another group examined 22 VS/UWS patients using a slightly modified version of oddball in which complex pattern deviations should be counted. A significant P3b to the counted stimulus was obtained in two

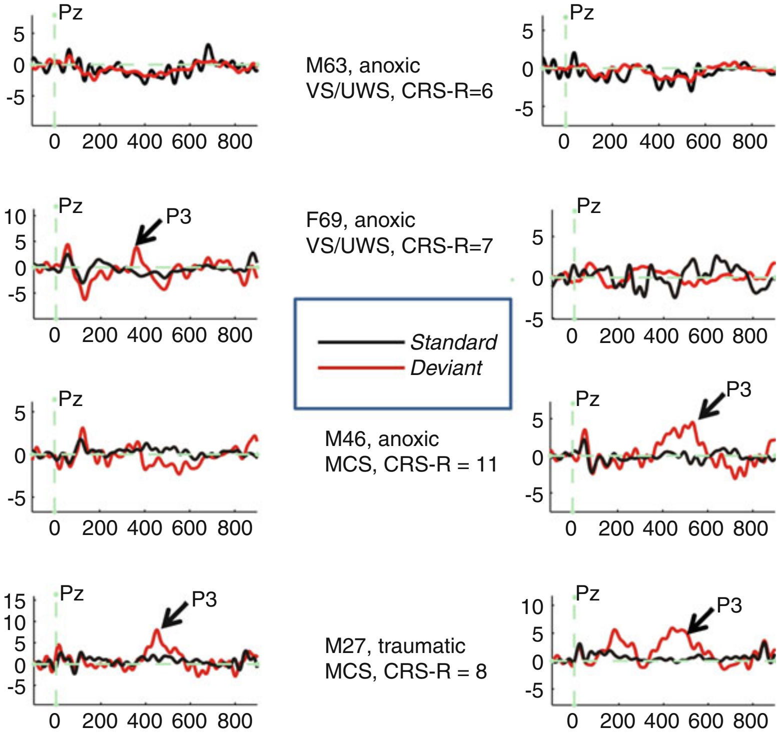

Fig. 9.3 Different outcomes of an oddball paradigm with two harmonic tones in four DoC patients. *Left column*: instruction "just to listen." *Right column*: instruction to count deviants. Negativity is plotted downwards. Pat. M63: no P3 in any condition. Pat. F69: P3 only in the passive condition. Pat. M46: P3 only in the active condition. Pat. M47: P3 in both passive and active conditions. *VS/UWS* vegetative/unresponsive wakefulness state, *MCS* minimally conscious state, *CRS-R* Coma Remission Scale-Revised, full score

patients whose diagnosis was changed to MCS within a few days after examination (Faugeras et al. 2011). In healthy individuals, this P3 response disappeared when they did not attend to the deviants (Bekinschtein et al. 2008), replicating the well-known attention effect on P3 (see above). Therefore, the positive findings in the two patients should be attributed to their following the instruction (i.e., the presence of active conscious intention) rather than to the nature of pattern deviation as such.

9.6 Diagnosis and Prognosis

As a common result of most studies, ERPs do *not* differentiate between VS/UWS and MCS (Balconi et al. 2013; Faugeras et al. 2011, 2012; Fischer et al. 2010; Kotchoubey et al. 2009; Perrin et al. 2006; Ragazzoni et al. 2013). Conclusions that "ERP were related to state of consciousness" should be taken with great caution. They are typically drawn either when taking into account conscious patients, in addition to VS/UWS and MCS, or when ERP effects coincide with some behavioral consciousness scale but *not* with the clinical borderline between VS/UWS and MCS (e.g., Wijnen et al. 2007). Two notable exceptions are Schoenle and Witzke (2004) and Schnakers et al. (2008), demonstrating large VS/MCS differences. In the former, however, the presence of ERP components was subjectively evaluated by a non-blinded rater. The latter included probably a particularly severe VS/UWS group, because even N1 was totally absent, although this component is typically recorded in most VS/UWS patients. Kotchoubey et al. (2005) data shed light on this issue. Most MCS patients have moderate (theta, 4–7 Hz) slowing of the background EEG oscillations (e.g., Leon-Carrion et al. 2008). If they are compared to VS/UWS patients with a similar EEG pattern, no difference in any ERP component can be found; however, VS/UWS patients with a severe slowing of the EEG rhythmic activity (delta, ≤3 Hz) do not demonstrate significant ERP components beyond (in a few cases) N1. Therefore, the results of other studies comparing

VS/UWS and MCS may critically depend on the exact "mixture" of VS/UWS patients with moderate versus severe background EEG disturbance in a particular sample (see also Chap. 5).

In contrast to the diagnosis, *etiology* seems to be a factor affecting ERP responsiveness in DoC. Particularly, late ERP components are more frequently found among traumatic patients than patients with anoxic brain injury (e.g., Cruse et al. 2012; Fischer et al. 2010; Kotchoubey 2005; Steppacher et al. 2013). The problem of diagnosis in DoC is closely related with that of *prognosis* (Bruno et al. 2011a; Gawryluk et al. 2010). Even taking into account important clinical variables such as etiology and time since the accident leaves a high degree of uncertainty. Therefore, a search for neurophysiological predictors remains an actual task.

Kotchoubey et al. (2005) retrospectively collected 6-month follow-up data in 23 VS/UWS and 20 MCS patients. Clinical improvement was observed in nine VS/UWS patients (four became MCS, five communicative) and ten MCS patients (all communicative). Patients who showed an MMN later improved significantly more frequently than patients without an MMN, and the same tendency approached significance for the N400. The importance of the MMN was confirmed by Dutch authors (Wijnen et al. 2007). Although they examined only ten VS/UWS patients, all of whom recovered, the study had several important advantages: it was prospective (rather than retrospective in Kotchoubey et al. 2005), the sample was homogenous, and each patient was examined every 2 weeks for a period of 3.5 months. The increase of MMN amplitude preceded clinical recovery, but the strongest change happened after the transition from VS/UWS to MCS, when the patients were able to inconsistent command following (in terms of Bruno et al. 2011b, the strongest MMN change coincided with the transition from MCS− to MCS+).

The MMN finding is noteworthy for two reasons. First, it reliably predicts the outcome of acute coma (Fischer et al. 1999; Daltrozzo et al. 2007) (see also Chap. 7). The acute pathological process in the brain and the chronic conditions such as VS/UWS and MCS differ substantially in their morphology and pathophysiology, and thus factors determining their temporal course are generally different. Nevertheless, the same ERP component may be an important index of brain function in both coma and chronic DoC. Second, the fact that the MMN predicts recovery of consciousness may appear strange, given that the component is largely independent of the actual state of consciousness. The presence of an MMN does not indicate that the patient is able to consciously perceive stimuli at the moment of examination but that this ability is not detected by clinical methods. Rather, the MMN may manifest the yet silent reserves of the brain that will later be realized in form of conscious awareness.

Several smaller studies can be mentioned here. In one of them, a young man with a traumatic VS/UWS was examined using ERP every 3–4 months. From month 6 post ictum, he regularly exhibited normal responses in both oddball (P3) and word pair paradigm (N400). The clinical condition did not change until month 22, when the patient suddenly regained full-blown awareness (Faran et al. 2006). Another study, already cited above (Faugeras et al. 2011), found two very recent (15 and 25 days post ictum) patients with a significant P3 to complex pattern deviation in a counting condition. Both patients developed an MCS within the next 7 days. No P3 in the same condition was obtained in 20 VS/UWS patients, only two of which changed to MCS in the next 7 days. Qin et al (2008) observed 3-month follow-up improvement in 4/9 patients with N1 and 0/3 patients without N1, as well as in 4/7 patients with an MMN to SON and 0/5 patients without the MMN. However, their sample also included patients in acute coma state. These data should be assessed as preliminary.

The predictive trend for the N400 observed by Kotchoubey et al (2005) was replicated in a recent study, the largest and most careful study to date (Steppacher et al. 2013). From the sample of 175 examined DoC patients, 53 VS and 39 MCS patients were followed up from 2 to 15 years (mean 8.3) after the accident. The target ERP components were determined using two methods: the most common visual expert assessment and the theoretically most informative *t-CWT*. Both methods yielded the same result: the presence of the N400 was strongly associated with clinical improvement during the following years (p-values between .0001 and .035). The predictive value of the N400 did not depend on diagnosis (VS/UWS, MCS) or etiology (traumatic, hypoxic, others). In contrast, the presence of oddball P3 was unrelated to the outcome in any diagnostic or etiological group (p-values between .35 and 1.0).

Contrary to the other reports, a significant predictive effect for P3 was found in a study with 34 traumatic VS/UWS patients (Cavinato et al. 2009), and for middle-latency auditory EP components in a study with 39 MCS patients (Luauté et al. 2010). In the latter study ERPs were recorded in the acute period, and the patients were followed up to 5 years. All of them were in MCS after 1 year (additionally, 12 VS/UWS patients were investigated, but none of them changed the diagnosis after 1 year). In the MCS group, N1 also contributed to the long-term outcome, but the MMN did not. Finally, Wijnen et al. (2014) were the only group who used visual (flash) stimulation in 11 VS/UWS patients und found a significant correlation between the expression of exogenous EP components and the clinical improvement 1 year later.

The lack of consistency in these data should not be surprising, as it has at least two reasons. First, the very large differences in patient samples: this concerns diagnosis (VS/UWS, MCS, coma), etiology (purely traumatic versus strongly mixed groups), and time post ictum (from few days in Faugeras et al. 2011 to several years in Luauté et al. 2010). This limitation also applies, however, in a least extend, to studies on correlates of cognition presented in Sect. 4, which might explain differences in the frequencies of ERP components. Second, and more specifically for prediction studies, the results critically depend on the initial set of independent variables which the search for predictors starts with. This set was rather small in all studies mentioned above. Including additional variables might radically change the final results. Reliable information on the predictive role of ERP and other neurophysiological variables (e.g., sleep EEG and fMRI) can only be obtained in a *large multicenter longitudinal study* involving a broad set of potential clinical, neurophysiological, and demographic predictors.

9.7 Conclusion

Event-related potential (ERP) represents a useful method for assessment of covert cognitive functions in patients with severe DoC. Having a poor spatial resolution as compared with fMRI and PET, ERPs possess a high level of functional specificity and an excellent temporal resolution, permitting to follow on-line information processing operations in the brain. ERP can be combined with different kinds of passive (pure stimulation) and active (instruction) tasks, which allows the investigator to check different cognitive abilities of the patients. Being a branch of the EEG, ERPs share all the advantages of the latter. The method is cheap, mobile, and well tested; all recordings can be done immediately at a patient's bedside. A very broad number of cognitive processes can be tested using ERP, most of which, however, are not necessarily related to consciousness. Although instruction tasks directly probing conscious awareness have also been used in combination with ERP, it should be further investigated whether ERPs have any advantages in instruction tasks as compared to fMRI (Monti et al. 2010), other EEG techniques (Goldfine et al. 2011), or even the simple electromyography (Bekinschtein et al. 2008).

A major limitation of the ERP methodology is a weak reflection of affective processes, an issue important from both theoretical and practical points of view. Many caregivers are primarily interested in such questions as whether their patients can feel pain and whether an emotional contact with them can be established. ERP can hardly shed light on the former question and rather limited in relation to the latter. Both pain and emotional perception are strongly mediated by the activity of deep brain structures that is not expressed in ERP components. On simple biophysical reasons, it appears highly improbable that ERP can manifest the activity of the insula, amygdala, or cerebellum. The activity of the anterior cingulate cortex, which also plays an important part in emotional processing, can be manifested in ERP (Nieuwenhuis et al. 2003; Cannon et al. 2009) but only in specific, very complex tasks that cannot be applied in DoC.

The following issues appear presently of major importance in ERP studies of DoC:

1. General assessment: How long should an ERP examination be, and how many stimuli have to be presented? The answer in basic studies is simply "the more, the better," but in DoC patients using too long paradigms can easily result in habituation and fatigue and thus in false-negatives. But how to determine the optimal length?
2. Assessment of consciousness: Can it be done in a passive paradigm? Active instruction tasks necessarily lead to false-negatives (Kotchoubey and Lang 2011), because many patients have conscious feelings but cannot follow instruction.
3. Assessment of prognosis: A large, well-controlled study with a representative DoC sample and a sufficient number of independent variables is necessary. Studies with a 10–50 patients and 5–10 independent variables appear of limited value.

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