Chapter 4
Electrophysiology in Disorders of Consciousness: From Conventional EEG Visual Analysis to Brain-Computer Interfaces

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Abstract Electroencephalography can offer many insights into brain activity useful for the study of disorders of consciousness. In this chapter, we will focus on the state of knowledge regarding the implementation of such a technique for diagnosis and prognosis in clinical setting, as well as the current effort for developing more reliable methods for assessing severely brain-injured patients with altered state of consciousness.

Electroencephalography

Electroencephalography is the measure of the brain's electrical activity using electrodes placed on the surface of the skull. It directly reflects neuronal activity with a high temporal resolution. However, the spatial resolution is poor for two main

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reasons: (1) it is limited by interelectrode distance, and (2) because of volume conduction, each sensor measures a sum of different brain sources; hence sensors have a correlated signal. The number of electrodes used depends on the application. For instance, when monitoring the level of anesthesia, only two electrodes are needed to obtain an electroencephalographic trace, while in clinical environments at least ten are used. In research, modern electrode caps have up to 256 electrodes. Electrode positioning on the cranial surface follows international nomenclatures (10-20 system for up to 19 electrodes and 10-10 system for more than 19 electrodes [1]), which aim to cover homogeneously most of the cranial surface. Electrodes are named according to their position on the scalp and have the letter F for frontal, C for central, P for parietal, O for occipital, or a letter combination such as FC for a position between frontal and central. Additionally, these letters are followed by a number (even for electrodes on the right hemisphere and odd for electrodes on the left hemisphere) or by the letter Z (for electrodes on the midline).

The measured signal results from a potential difference between two electrodes. It is, therefore, not possible to use only one electrode. There are two categories of montages: bipolar montages in which the electrodes are paired two by two and referential montages where all the electrodes are coupled to a single electrode called the reference. In a bipolar montage, it can be considered that the recorded signal stems from an imaginary position located between the two electrodes. In a referential montage, the reference should not be located in a region where a signal of interest has to be recorded. Common positions for the reference are the earlobes; the mastoids, possibly coupled; the nose; or a position on the midline. The choice of the reference electrode has an influence on the shape of the recorded signal, notably for evoked potentials. Bipolar montages are less sensitive to artifacts but will not detect events that are common to two coupled electrodes. A referential montage does not have this drawback but is, however, more sensitive to artifacts [2].

The electroencephalogram (EEG) does not only detect electrical fields generated by cerebral activity but also fields generated by muscular activity such as eye or eyelid movements or fields generated by electrical apparatus. Patients in altered states of consciousness are often surrounded by many different electronic equipment withstanding their vital functions. They have little control of their movements and can be spastic. Furthermore, they do not control their level of sudation, which can potentially be the cause of artifacts, which should be minimized during the recording. It is a good practice to simultaneously record respiration, heartbeats, and muscular activity in order to better track artifacts and eventually remove them from the signal. It is also important to have full knowledge of all drugs prescribed to the patient as some can have a sedative effect, which can result in a slower EEG, or others such as benzodiazepines can add additional fast frequencies to the signal. Some artifacts can be eliminated by data filtering. A notch filter removes the 50 Hz line noise (60 Hz in the United States and other regions in the world). The EEG spectrum covers frequencies ranging from less than 1 Hz to several hundreds of Hz. The use of filters should, therefore, depend on the frequency bands of interest. Too much filtering of low frequencies might hide slow-wave activity, while filtering high frequencies might hide spindles and spike waves. Heavy filtering results in a clean EEG trace but might remove some of the signal of interest [2]. Taking these

considerations into account, the EEG signal is often observed after filtering between 1 and 30 Hz, notably in sleep studies or for evoked potentials. These limits can then be adjusted in order to include more frequencies.

The electroencephalography (EEG) has a long history of use in the intensive care unit, and there is a well-documented literature on EEG abnormalities in comatose patients and patients in unresponsive wakefulness syndrome (UWS). Less is known about EEG activity in acute patients in minimally conscious state (MCS). The traditional visual inspection of the EEG is more and more complemented by event-related potentials. In parallel, researchers are developing new paradigms to probe higher and higher cognitive functions. New quantitative tools are developed to ease the interpretation of the EEG.

Clinical EEG

A routine clinical EEG recording usually lasts 20–30 min without stimulations to properly assess EEG background activity and to detect potential changes [3], and EEG reactivity should also be assessed, unless there is a concern of raised intracranial pressure due to stimuli [4]. Sufficient length of recording is necessary to ensure a reliable interpretation despite the presence of artifacts (e.g., electrode failure, movement or sweat artifacts) that could lead to undetectable physiological or even pathological events. The visual interpretation of an EEG trace gives information on the global cerebral activity of a patient.

Acute Stage

EEG Visual Analysis

In the acute stage, the EEG can help to establish the origin and the severity of the injury (e.g., in the case of a focal lesion or a diffuse dysfunction) and differentiate states that are symptomatically similar to coma such as an epileptic absence, a psychogenic coma, a noncooperative patient, or a locked-in syndrome (LIS). Combined with the etiology, the EEG can give an indication on the patient's prognosis. Finally, the EEG can track the patient evolution and the effect of drugs such as antiepileptics and sedative [3, 5, 6].

The EEG is useful for detecting and managing epileptic spikes, nonconvulsive epileptic seizures, or nonconvulsive status epilepticus [6]. Synchronized video recordings are strongly recommended as they provide useful information for identifying artifacts and getting further insights in case of seizure [7]. A nonconvulsive epileptic seizure does not present the usual signs of a complex partial seizure like oculomotor and masticatory muscle contraction, and the patient can appear confused, drowsy, or comatose. The EEG will show a continuous epileptic activity. Nonconvulsive seizures are present in 18–37% of patients in ICU [8, 9].

Management of epileptic activity is particularly challenging as delayed treatment of an ictal pattern may lead to difficulty in controlling a seizure or may result in further brain damage. Conversely, inappropriate use of antiepileptic drugs may lead to increased sedation, while overly aggressive treatment may result in complications due to side effect and pharmacokinetic interactions [10]. Furthermore, in acute comatose patients, the determination of truly epileptiform activity is also challenging. A patient with epileptic activity not responding to administered antiepileptic drugs and without possibility to treat the cause of the seizures has a poor prognosis [11].

Following a brain injury, whether it is of traumatic or anoxic origin, the EEG can be significantly abnormal. Different types of abnormalities can be observed, such as polymorphic delta activity, or epileptic spikes can display alterations and abnormalities. These abnormal EEG patterns allow to assess the severity of the coma and are related to prognosis. Based on previous work by Hockaday et al. [12], Synek et al. [13] suggested a scale classifying these patterns according to their prognosis. This scale has then been adapted by Young et al. in order to improve its reproducibility [6]. Young's scale is presented in Table 4.1 and gives information on the level of the coma. The higher the grade, the deeper the coma. Grade 1 corresponds to a slowing down of the EEG in comparison to a healthy subject. The slowing of the brain activity is proportional to the severity of the injury. The predominant rhythm is no longer the posterior alpha (8–12 Hz) present in healthy subjects but diffuse theta (4–7 Hz) or delta (1–3 Hz). If there is asymmetric brain damage, the EEG will likely also be asymmetric; the EEG above unaffected area can appear almost normal whereas that above affected area is severely impaired. Nevertheless, a precise location of a lesion cannot be achieved with the EEG as its spatial resolution is low [3].

Table 4.1 EEG classification of acute patients introduced by Young and collaborators [6]

Category	Subcategory
1. Delta/theta >50% of record (no theta coma)	(a) Reactivity
	(b) No reactivity
2. Triphasic waves	
3. Burst suppression	(a) With epileptiform activity
	(b) Without epileptiform activity
4. Alpha/theta/spindle coma (unreactive)	
5. Epileptiform activity (no burst-suppression pattern)	(a) Generalized
	(b) Focal or multifocal
6. Suppression	(a) <20 μV but >10 μV
	(b) <10 μV
Guidelines	
1. Burst-suppression pattern should present generalized flattening at standard sensitivity for more than 1 s at least every 20 s	
2. Suppression: for this category, voltage criteria should be met for the entire recording; there should be no reactivity	
3. When more than one category is present, select the most critical one	

It is important to test the reactivity of the EEG to eye opening/closing and external stimulations. A reactive EEG reflects a lighter coma and is associated with a better prognosis [3, 6, 14, 15]. Auditory or nociceptive stimulations can be used and should be performed 20–30s apart. A clear reactivity is a reproducible change in the background frequency and amplitude [15].

Higher grades are related to the apparition of specific patterns. Grade 2 corresponds to the occurrence of triphasic waves, that is, sharp deflections with two or three phases, the second phase having the highest amplitude. Grade 3 is related to burst-suppression pattern. Bursts of slow waves mingled with high frequency transients are followed by periods of flat EEG. In some cases of severe brain lesions, some comatose patients can display an EEG that is comparable to a normal wake EEG with a predominant alpha or theta rhythm but distributed differently to healthy subjects, as it is more frontally distributed—the alpha/theta coma (Grade 4). In the case of an alpha/theta coma, EEG does not react to stimulation according to most authors [6, 16] but not all [3, 17]. These patients must be differentiated from patients suffering a LIS or patients in a psychogenic coma. Indeed, in both the latter cases, the EEG can be close to normal [3]. The presence of epileptic activity despite antiepileptic medication corresponds to Grade 5.

The last stage of the coma is characterized by suppression (Grade 6), when there is no cerebral activity higher than 2 μV. An inactive EEG that lasts for more than 6 h in a patient who is not in hypothermia suggests prosencephalon death but not necessarily cerebral death as the EEG does not reflect the activity of the brainstem [5]. In some rare occasions, patients in "permanent vegetative state" can have an inactive EEG [3]. Similarly, drug intoxication can lead to an inactive EEG, but it is often reversible.

The interpretation of an EEG recording does not allow a prognostic statement if it is not combined with the etiology. Indeed, the characteristic features of the EEG are not specific to one etiology. Here are some examples of poor prognosis. In case of a cardiac arrest, a periodic generalized pattern is of poor prognosis. Following a hypoxia or metabolic encephalopathy, the apparition of suppression periods lasting several seconds that are not followed by a burst is of poor prognosis. A pattern such as alpha coma or alpha/theta coma is associated with different prognoses based on the etiology. For instance, if it is associated with a brainstem lesion, it is of poor prognosis. Importantly, to be of prognostic value, an EEG recording should not be done too early after the beginning of coma [13]. For a detailed review of prognosis associated with different patterns, we recommend the article by Brenner [3] or the chapter by Rossetti [15].

Evoked Potentials

Evoked potentials are components of the EEG obtained in response to particular events or sensory stimulation. They reflect the processing of the stimulus through time, from low-level peripheral receptive structures up to high-level associative

cerebral areas. The faster components, linked to the physical properties of the stimulus, are called *exogenous* and reflect the activation of neurons projecting toward the primary cortex. Belated components are linked to the psychological significance of the stimulus, the experimental conditions, and the level of awareness. They are called *endogenous* components and reflect the activity of subcortical and cortical structures, including associative areas. Evoked potentials allow an objective evaluation of patients' sensory, motor, and cognitive functions.

Somatosensory evoked potentials (SEPs) are obtained by transcutaneous electric stimulation of median nerves in the wrist. These potentials reflect the conduction of the nervous influx through the brachial plexus and its access to the primary somatosensory cortex [18]. A bilateral absence of the N20 in a comatose patient following circulatory arrest is highly associated with an absence of consciousness recovery (in 99–100% of cases) [19–22]. For other etiologies, the absence of SEP does not convey strong prognostic information. In traumatic brain injury, the absence of SEP could be due to a focal midbrain dysfunction or a focal cortical lesion [23] and is not a reliable predictor of poor prognosis [24]. In ischemic or hemorrhagic stroke, the absence of SEP correlates with poor outcome [25, 26]. In sepsis and septic shock, the patients often present delayed SEP peak latencies, but SEP does not help establishing a prognosis [24].

Brainstem auditory evoked potentials (BAEPs) are useful to study the conduction of the auditory signal via the auditory nerve and the protuberance. They appear within 10 ms. The absence of these potentials is associated with a poor recovery in patients with severe cerebral lesions but without peripheral auditory lesions [27, 28]. Nevertheless, this component has a lower predictive value than the N20 response [20]. Visual evoked potentials elicited by flashes are less common because they do not always trigger a response, even in healthy controls [29].

If the absence of exogenous components is often associated with a poor prognosis [30], the presence of exogenous components is not informative enough to be a marker of good prognosis. Clear exogenous components can be observed in patients that never recover.

More advanced cerebral processes, possibly reflecting the presence of consciousness, can be studied using cognitive evoked potentials. Until now they were exclusively studied with auditory tasks because comatose patients do not have eye-gaze control. They differ from exogenous evoked potentials in the sense that they are highly dependent on the experimental conditions. It is, thus, important to record these potentials when the patient is most vigilant and to ensure that the paradigm is optimized for recording the best potentials while minimizing the number of repetitions to avoid a habituation effect. Three components have been studied in acute patients: the N100 component in response to a stimulus, the mismatch negativity and the P3 in response to novelty, and the N400 and P600 components in response to semantic changes. Despite the fact that the presence of one of these components is related to good prognosis, they are less often recorded in acute patients. We believe that the main reasons for their limited use are the lack of clear guidelines to record these potentials, the influence of patient's fluctuations of vigilance on the components, the difficulty to assess the presence of a component, and the lack of

cohort studies relating these components to prognosis. The interpretation is especially problematic. Exogenous potentials are repeated hundreds to thousands of times with always the same "response." Endogenous potentials are repeated tens to hundreds of times with several factors influencing each repetition giving rise to slightly different "responses." To overcome these limitations, classic research average "response" over repetitions and over subjects leading to group average. This approach is not suitable for individual diagnosis or prognosis. To interpret the component waveform, researchers rely on several approaches balancing statistical test and a priori information on the location and latency of the component. Using too strict prior on location and latency may be problematic as brain damage may induce delayed latency and prevent the potential to be found above damaged areas. The statistical test should be strict enough to avoid false positive but flexible enough to detect weak component. Most groups use a different approach as no gold standard approach has been proposed yet.

The N100 component, a negative inflection that appears 100 ms after the start of the stimulus, indicates a response of the auditory cortex. This component is elicited by all types of stimuli and reveals that the auditory cortex is properly functioning. Its predictive value is, however, highly debated [31–34]. Aside from BAEPs, the N100 component would yet have a lower predictive value than the N20 response as regards consciousness recovery in comatose patients [20, 32, 33].

The mismatch negativity (MMN) is a negative component, which appears between 100 and 200 ms after a change or odd sound following a series of monotonous sounds. This component has low amplitude, which implies that a high number of repetitions are necessary for a good visualization. Since the MMN does not require the subject's attention, it indicates an automatic response triggered by the difference between the dissonant sound and the other preceding sounds which are still recorded in memory. Previous data obtained with an MMN paradigm in comatose patients suggest that this component beholds important predictive value independent of the etiology. Indeed, the presence of this response was related to very high probability of awakening [20, 31, 35–38].

The P3 is a positive inflection generated when the subject detects a rare and unexpected stimulus. For an auditory potential, it appears approximately 300 ms after the stimulus, while for a visual stimulus, it can appear 500 or 600 ms after the stimulus presentation. In case of cerebral lesions, its latency can be higher [39, 40]. The MMN and P3 are two different cerebral responses elicited by similar stimuli (deviant or novel), but they differ according to the time interval between stimuli. The MMN is generated when the stimuli are close to one another but disappears when the interval between two stimuli is longer than 2 s. The MMN originates from the superior temporal gyrus and from the frontal cortex. The P3 relates to the activation of a network of cerebral areas including frontoparietal regions [41]. The P3 is frequently linked to cognitive processes of higher complexity than the N100 and MMN components, such as categorization, decision-making, or updates in working memory. If simple sounds are sufficient for the generation of an MMN or a P3, the latter can also be generated by more complex stimuli. The emotional valence of these stimuli will have an impact on the amplitude. A stimulus such as the own

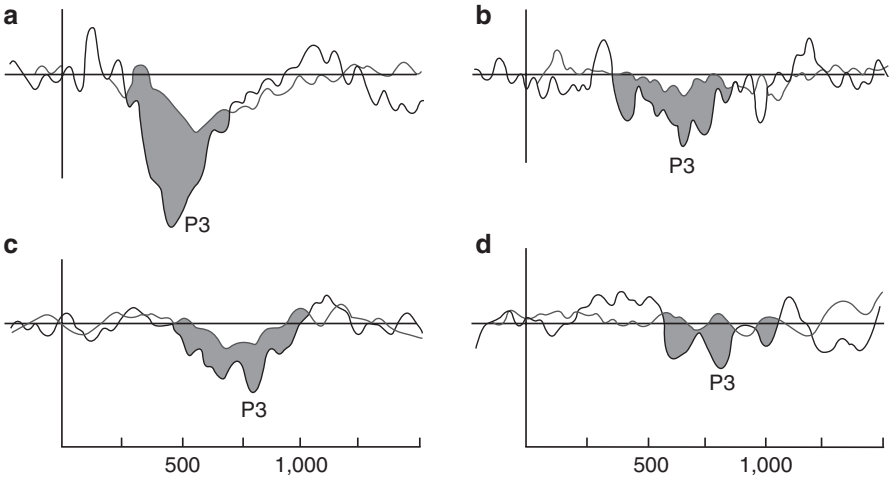

Fig. 4.1 Auditory evoked potentials in response to the own name in (**a**) healthy controls ($n = 5$) and (**b**) patients with a locked-in syndrome ($n = 4$), (**c**) with a minimally conscious state ($n = 6$), and (**d**) with an unresponsive wakefulness syndrome ($n = 5$). The area in *gray* represents the difference in activation between the presentation of the own name and the presentation of other names. A P3 response can be observed even in some patients in a vegetative state. Electrode Pz (Adapted from [30])

name will more likely trigger a P3 than a simple sound [42, 43] (Fig. 4.1). The presence of a P3 is related to good prognosis, but its absence does not convey any information [33, 44–46].

Quantitative EEG

Quantitative electroencephalography (QEEG) consists in the use of algorithms in order to extract complex measures likely to add objective information that can simplify the visual inspection of the EEG traces. For instance, one can compute the power spectral density of the signal at each electrode location to detect background rhythms, automatically detect epileptiform activities, or detect the presence of event-related potentials. Inherently, QEEG is less subjective than the visual analysis of the raw EEG signals and has been shown to offer better validity than visual scoring [47]. QEEG also facilitates the analysis of long-term EEG monitoring [48] or the repetition of recordings. Interestingly, the difference between two recordings in acute stage has been shown to be a good predictor of outcome in comatose patients [37, 49].

Automatic analysis of background EEG and reactivity has been proposed with methods based on burst-suppression ratio, entropy, or amplitude equivalent EEG or frequency decomposition and has shown to have prognostic implications [50–53].

The presence of event-related potential components has been investigated with machine learning [49, 54, 55]. Machine learning techniques are not biased by a priori hypotheses regarding electrode locations or latency of the components. Compared to the traditional techniques in this domain, they are also less affected by transient, artifact-contaminated activity recorded at certain electrodes. Furthermore, they provide a way to quantify differences in neural responses at the level of the single patient [49].

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Chronic Stage

EEG Visual Analysis

Recent studies have shown the interest of traditional EEG visual analysis for diagnosis in chronic severely brain-injured patients when describing EEG features according to standard clinical neurophysiological recommendations [56]. A recent work proposed a classification of the EEG of patients with DOC and compared it with behavioral testing and fMRI-based command-following [48]. They showed a significant correlation between the abnormality of the EEG and behavioral testing. Furthermore, all four patients showing fMRI evidence of command-following in the study also demonstrated well-organized EEG background during wakefulness and spindling activity during sleep, highlighting that EEG can be used as a complement to behavioral assessment for detecting the likelihood of unrecognized cognitive abilities in chronic DOC. Another study adapted the classification scheme (Table 4.2) and further demonstrated the usefulness of conventional EEG to disentangle patients in a chronic UWS from a MCS− and MCS+, with a better diagnostic reliability for traumatic patients than anoxic ones [57].

Table 4.2 EEG classification of chronic patients used by Estraneo and collaborators [57]

Category	Description
Normal activity	Predominant posterior alpha, anterior-posterior gradient, without focal or hemispheric slowing or epileptiform abnormalities
Mildly abnormal	Predominant posterior theta, symmetric or not, with frequent posterior alpha
Moderately abnormal	Predominant posterior theta, symmetric or not, with rare or occasional alpha, poorly organized anterior-posterior gradient
Diffuse slowing	Predominant diffuse theta or theta/delta, without anterior-posterior gradient
Low voltage	Predominant diffuse and low theta or delta (<20 μV)

Evoked Potentials

In acute patients, evoked potentials are used for their prognostic information. In chronic patients, researchers have studied their diagnostic power and concentrate their researches in finding the relationship between cognitive event-related potentials and patients' state of consciousness. Exogenous potentials are not very informative in chronic condition except that their absence prevents the interpretation of latter cognitive event [58].

At the group level, Kotchoubey et al. have shown that the MMN component could be present both in MCS patient (34%) and in UWS patients (65%) [59]. Interestingly, Wijnen et al. demonstrated that for ten UWS patients, the amplitude of the MMN was significantly higher in patients who evolved later to a MCS [60].

From a behavioral point of view, the distinction between these two states can be made based on response to command. Hence, active evoked potentials are used to better evaluate consciousness in a patient as it requires his/her active participation, which differs from passive listening. In a study, patients were asked to count occurrences of their own name, presented along with seven other names; some MCS patients displayed a P3 of greater amplitude than when passively listening to their name. On the other hand, UWS patients who showed a P3 in response to their name did not display higher amplitudes when asked to actively count their names [43]. This paradigm confirmed the presence of conscious processing in a LIS patient [61]. However, one study reported increased P3 amplitude in behaviorally unresponsive patients during active task based on a deviant tone [62]. An extensive research on attention involving healthy subjects has suggested that the P3 response should be decomposed into separable subcomponents called the P3a and P3b. The relatively early, frontally located P3a is thought to reflect exogenous attention, triggered by "bottom-up" stimulus novelty that may be task irrelevant. The later, parietally centered P3b, on the other hand, is suggested to be a marker of "top-down" or volitional engagement of endogenous attention to task-relevant targets to be consolidated into working memory and made available for conscious access. Chennu et al. [63] developed a task designed to engender such exogenous or endogenous attention, as indexed by the P3a and P3b components, using pairs of word stimuli presented auditorily among distractors. Results suggested that bottom-up and top-down attentional processing might be preserved in some patients in a MCS and UWS. However, the level of difficulty required by this task seems to be too high to enable a good rate of detection of conscious patients.

In the same idea, another study used a different auditory P3-based paradigm based on tone stream segregation allowing for binary decisions [64] in a small cohort of chronic DOC patients. Two tone streams with infrequently and randomly appearing deviant tones were presented to the patient. The patient was asked to count the number of deviants in one stream, in order to modulate the P3 response to the attended stream. Only five patients could achieve results above chance level, and none of them achieved performances allowing communication with the system.

Another auditory paradigm assessed the participant's ability to pay attention to global violations of temporal regularities, the local-global paradigm [65–67]. This paradigm involves sequences of auditory stimuli of either identical tones, called locally standard, or identical tones and a deviant tone, called locally deviant. Here, the term "local" refers to a single sequence. The locally deviant sequences typically lead to a MMN. Alternatively, the term "global" refers to irregularities between sequences. For example, if 80% of sequences are locally deviant, these are the ones considered globally standard, while the remaining 20%, which are locally standard, will be the globally deviant sequences since these are the minority. Global deviant sequences generate a late P3b response. When tested on patients, this paradigm had 34% sensitivity of detecting the ability to follow a command and 88% specificity.

Another candidate biomarker of consciousness is the N400, a negative inflection which appears roughly 400 ms after a word presentation. Its amplitude is increased if the stimulus is discordant (semantic or phonologic discordances) based on the context (word or sentence). Care must be taken, however, as a semantic incongruence can also lead to a P600, a positive inflection which appears 600 ms after stimulus presentation. Any change, negative or positive, can, thus, be considered as incongruence processing. These inflections have been found in MCS and UWS patients preventing their interpretation as a diagnosis marker [68, 69]. However, their presence has been suggested as a marker of good prognosis in less than a year patients [69].

Evoked potentials are complementary to behavioral studies in patients. It was first suggested to present them in a hierarchical approach [70] where low-level functionalities are first evaluated with exogenous potentials and then higher-level processing is tested with cognitive potentials. The latter is presented in passive and then in active tasks. However, recent researches tend to show that patients may present a response to an active paradigm while no activation was detected with a passive paradigm. Active paradigms may therefore convey more information than the passive ones. If the patient answers to the active task, this is suggested to be equivalent to a behavioral response to command. At this stage, it becomes important to test communication tools with the patient such as brain-computer interfaces (see below).

Background Rhythms, Connectivity, and Complexity

The quantitative EEG analysis has shown a slowing down of the EEG in patients with DOC in comparison to healthy participants, more marked in UWS than in MCS patients [71, 72]. UWS and MCS patients showed an increase of delta power and a decreased alpha power. Such findings can also be observed through visual analysis of the EEG traces (Fig. 4.2) [71, 73].

The EEG can also help to quantify the functional connectivity between cerebral areas [74]. PET and fMRI studies have reported a disrupted functional connectivity in patients suffering from disorders of consciousness [75–78]. Computing the coupling between electrodes provides a connectivity measure of underlying brain areas.

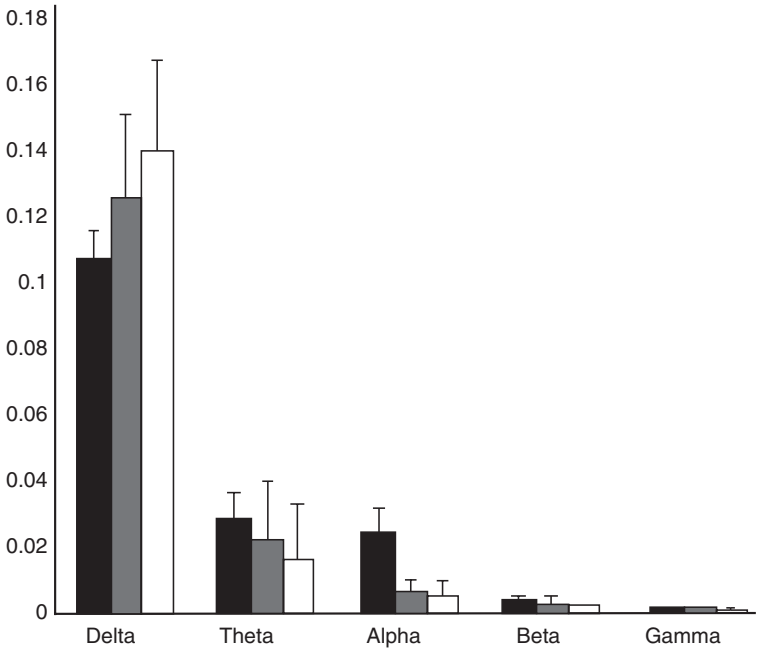

Fig. 4.2 Normalized power spectral density computed at Cz in five different frequency bands in healthy controls (*black*; $n = 5$), patients in a minimally conscious state (*gray*; $n = 12$, MCS), and patients in an unresponsive wakefulness syndrome (*white*; $n = 10$, UWS). Patients with disorders of consciousness have more power in low-frequency bands and less power in higher-frequency bands, suggesting a slowing down EEG activity

This measure gives complementary information that can be used for diagnostic and prognostic purposes. A study on a single patient with UWS with right hemisphere lesion showed a diminution of the functional connectivity in the damaged hemisphere. Such decrease was not visible using spectral power measures [79]. Group studies confirmed the decreased connectivity in patients with UWS and showed a slighter decreased functional connectivity in patients with MCS [71, 80–82].

Tools based on the complexity of the signal and initially developed for anesthesia monitoring have been proposed to evaluate the level of consciousness in severely brain-injured patients. These tools are used in the clinical field to measure the depth of anesthesia and to prevent the patient's arousal during a surgical procedure, while allowing drug savings and a faster postoperative awakening, thanks to a better control of the depth of anesthesia. Furthermore, they are easy to use and interpret. For example, the bispectral index (BIS) is a unitless measure ranging from 0 (inactive EEG) to 100 (normal activity), which results from a combination of temporal and frequency parameters [83]. BIS values correlate with the decrease of vigilance observed during the different sleep stages [84]. In case of disorders of consciousness, UWS patients have a lower BIS value than patients in a MCS, but this value cannot systematically differentiate patients in a UWS from patients in a MCS at an individual level [85]. Similar results were obtained using the EEG spectral entropy [86, 87].

These results were obtained at group level. Individual BIS or entropy values are not accurate enough to establish a diagnosis in chronic stage.

The potential of EEG frequency power, functional connectivity, and complexity are also highlighted by the results of machine learning studies. They are reliable measures to differentiate between UWS, MCS, and conscious participants according to a cohort study involving 113 patients [54]. Functional connectivity is the best measure distinguishing MCS from UWS in another cohort of 54 patients [88].

Long-Term EEG: Polysomnography

Sleep is characterized by behavioral decreases in vigilance as characterized by the presence of eye closure and muscle inactivity, as well as a number of electrophysiological features such as slow waves, spindles, and rapid eye movement and non-rapid eye movement [89]. These sleep patterns may be an adaptive phenomenon to maintain global brain integrity as they have been shown to be altered in pathologies such as stroke [90] and Alzheimer's disease [91]. A better understanding of sleep cycles and architecture of patients with DOC might therefore provide useful information about diagnosis and prognosis in this population [92].

In 2011, Landsness et al. studied sleep pattern using EEG high density in 11 patients with DOC [93]. They reported that clear EEG changes could be observed by visual analysis in all MCS patients during decreases in behavioral vigilance. In addition, the majority of these patients had several EEG features typical of normal sleep (i.e., all patients showed an alternating non-rapid eye movement/rapid eye movement sleep pattern and a homoeostatic decline of EEG slow-wave activity through the night). On the other hand, even though preserved behavioral sleep was observed in all UWS patients, no clear changes were observed during periods of eye closure as compared with periods with eyes opened. In particular, no slow-wave sleep or rapid eye movement sleep stages were identified, and no homoeostatic regulation of sleep-related slow-wave activity was observed. This study supports the relationship between sleep electrophysiology and the level of consciousness in patients with DOC, and sleep study could help improve the diagnosis of these patients.

These findings were then supported by other studies performed elsewhere also reporting the importance of preserved sleep patterns for consciousness [48, 94], some of them also reporting the potential prognostic value of the presence of specific features (i.e., sleep spindles) for further recovery of consciousness [95, 96].

Electromyography

Bekinschtein et al. studied DOC patients using electromyography (EMG, recording of muscle activity) [97] to detect signs of command-following unobservable with the naked eye. They presented four different 30s—blocks of commands to the

patient, “Please try to move your right hand” and “Please try to move your left hand,” and two control phrases, “Today is a sunny day” and “It is raining outside today.” At the end of the block, the instruction was “Please do not move, stay still.” They observed an increased EMG signal specifically linked to command in several cases of patients in a MCS or UWS, suggesting that EMG could be used to objectively detect subthreshold motor response in this population.

Following this work, Habbal and colleagues [98] used a similar method to investigate the impact of the type of movements used (i.e., “Move your hands,” “Move your legs,” and “Clench your teeth”), on a bigger cohort of patients. Supporting previous results, they reported willful EMG responses in a small group of patients. In addition, they observed a better response with the stimulus “Move your hands” in both healthy controls and patients, confirming that EMG could help to detect voluntary movements in this population. Finally, Lesenfants and colleagues [99] proposed a new methodology based on single-trial analysis for detecting residual response to command with EMG in patients with DOC. The use of single-trial evaluation of response to command allows to overcome the issue of trial dependency and decrease the influence of a patient’s fluctuation of vigilance or arousal over time on diagnostic accuracy. They illustrated a response to command in all MCS cases displaying reproducible response to command at bedside on multiple assessments, even though only 6 of the 14 individuals presented a behavioral response to command on the day of the EMG assessment.

Brain-Computer Interface

A brain-computer interface (BCI) is a system allowing for communication between the brain and the external environment. It is independent from any peripheral neural or muscular activity, and it directly converts brain activity into a computerized command [100]. BCIs could be of interest particularly for communicating with patients whose cognitive functions are intact but are paralyzed and anarthric following a neurological or muscular damage, e.g., patients with a LIS [101]. These patients will present a normal EEG or a response to an active paradigm. Simple augmentative and alternative communication tools have been developed to allow communication with these patients. The simplest are based on the tracking of residual motor function such as head or eye movements [102]. Character’s selection is made with dwell, physical click, or blink. For people with severe motor disabilities, a simple yes-no communication can be achieved [e.g., one eye blink for yes, two blinks for no]. However, these methods are based on the patient’s residual motor ability. In some cases, it is necessary to use a communication system that does not involve motor skills at all. Those motor-independent systems are not only useful for using alphabetic systems and expressing more complex ideas [103]. BCIs could be the key to providing access to the outside world for a LIS patient [104]. Finally, beyond

communication, BCIs have also inspired new approaches to detect a response to a command in the absence of discernible behavior at the bedside [105].

A BCI is based on cerebral activity measured using techniques, such as electroencephalography (EEG), functional magnetic resonance imagery (fMRI), implanted electrodes (intracortical recording or electrocorticography), or functional near-infrared spectroscopy (fNIRS) in order to control the environment [106]. A BCI is not a "mind-reading" device. Its primary function is to decode brain activity and map it with a set of continuous or discrete selections to allow a subject to choose between different options. This choice is made through the control of neuroelectrical activity in real time [107–109]. A specific algorithm translates the extracted features into commands that represent the user's intent. These commands can control effectors to select items (e.g., words). Recent development has shown the usefulness of BCIs in controlling motor prosthesis, cursors, access to internet, and communication [109–114]. Here, we will focus on systems allowing functional communication with the surrounding and will present the recent progress in the development of BCIs. Moreover, we discuss clinical applications in LIS patients and studies performed in patients recovering from coma.

EEG-Based BCI

EEG-based BCI paradigms have been developed through testing with healthy controls and severely motor disabled (LIS, e.g., amyotrophic lateral sclerosis (ALS) [109, 115]) and more recently with patients with DOC. EEG-based BCIs use ERPs, more precisely components such as the P3 or steady-state visually evoked potentials (SSVEPs), sensorimotor rhythms (SMRs), slow cortical potentials (SCPs), and the alpha rhythm. Studies usually report a great heterogeneity in the results depending on the population, the method (from the cognitive task to data analyses), and the modality involved.

The most widely used ERP component is the P3. Donchin and his colleagues have developed a visual BCI using a 6 × 6 matrix composed of letters and signs [116]. The rows and columns are successively illuminated. The participant has to focus his/her attention on the letter he/she wants to spell, eliciting a P3. With this type of BCI, users would be able to spell up to 7–8 letters per minute with an accuracy of 80–90%. One study showed that it was possible to establish communication [115] in five out of six ALS patients using this visual P3-based paradigm developed by Donchin [116]. Four of them could use the system later for spelling words and demonstrated functional communication. As visually based BCIs could be hard to implement in patients with gaze control impairment, Kübler has adapted the use of a matrix in the auditory modality. Five rows and five columns represented the letters of the alphabet [117]. The five lines were associated with a number between 1 and 5 and the five columns with a number between 6 and 10. The numbers were

auditorily presented and the patient selected the row and the column of the target letter. Four ALS patients were evaluated with this system, demonstrating adequate performance for visual (more than 70%) but not for auditory (just above chance level) communication. Moreover, users reported more difficulty to concentrate during the auditory condition.

Lugo and colleagues investigated the use of a vibrotactile paradigm to trigger P3 responses in patients with LIS for establishing somatosensory BCI-based communication. They were asked to first count a target stimulus and then answer five questions by counting the vibrations on either the right wrist for "yes" or the left wrist for "no." Four patients achieved 100% accuracy during the counting task, whereas one patient achieved 100% accuracy during the communication. These findings support the feasibility of eliciting a P3 response using vibrotactile stimulation in patients with LIS. This approach is currently tested for the detection of consciousness in DOC, but no results have been published at this moment.

To our knowledge, Lulé et al. performed the first study in patients with DOC [118]. They used the Sellers and Donchin's P3 paradigm using auditory stimuli (yes, no, stop, go) [107] to test its reliability as a diagnostic tool for DOC. If the study showed the feasibility of applying a BCI system in chronic patients with DOC, only one MCS and one LIS patient achieved offline performance above chance level suggesting a response to command (Fig. 4.3). These results suggest that the BCI system cannot ensure the absence of consciousness in case of negative results [118], especially as the use of such paradigms may be limited by the patient's sensory impairment (e.g., auditory, visual).

Finally, Chatelle et al. [119] investigated the applicability of a visual P3-based and an SSVEP-BCI to communicate with patients with incomplete LIS by looking at BCI performance, mental workload, and overall satisfaction with both systems. If all of the seven patients included were able to achieve an accuracy of 70% or higher with the SSVEP-based BCI, only three patients could achieve that with the P3-based BCI. In addition, the SSVEP-based BCI was associated with a lower mental workload and a higher overall satisfaction, suggesting that the SSVEP might be more suitable for patients with severe motor disabilities. On the other hand, such SSVEP paradigms are highly dependent on eye movements, which can be very limited in patients with DOC. To overcome this issue, Lesenfants et al. [120] developed a gaze-independent SSVEP-BCI based on covert attention. Two out of the six LIS patients included could reach accuracy above chance level offline, illustrating a response to a command, whereas one patient could communicate online, suggesting that covert SSVEP is feasible but there is a clear need for further improvement in order to provide more sensitive tools that could be used for diagnosis and/or communication in severely brain-injured patients.

Changes in SMRs or μ rhythms have also been used for BCI purposes. SMRs refer to EEG activity of 8–15 Hz that can be recorded in primary sensorimotor areas [100] and which is usually accompanied by a beta activity (18–26 Hz). This activity can be reduced or desynchronized by preparing, executing, or imagining a movement (event-related desynchronization), particularly in the contralateral motor

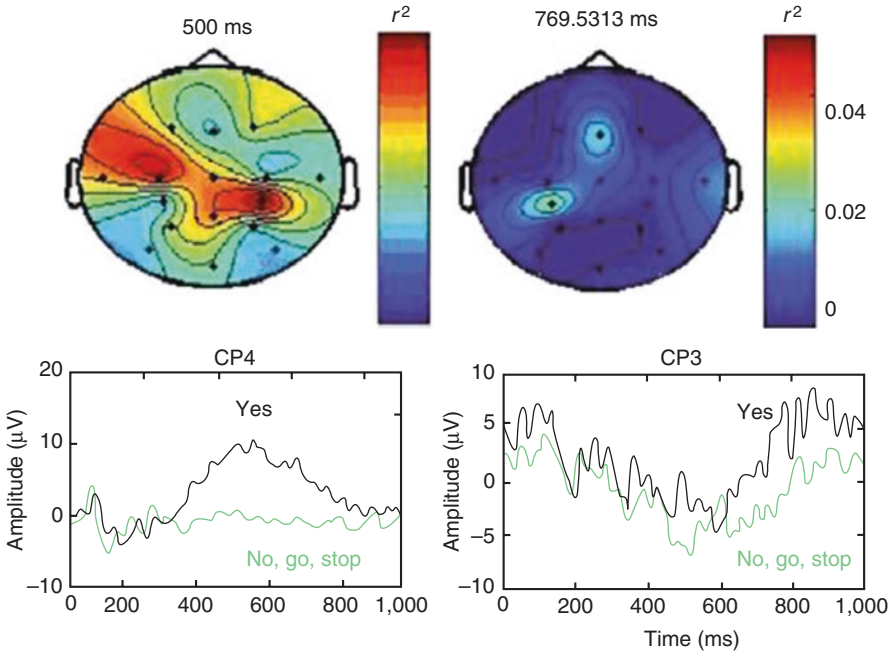

Fig. 4.3 P3 in a healthy volunteer (*left*) and a patient in a minimally conscious state (*right*) in response to the target stimulus *yes*. On the *top*, distribution of the observed response to target stimuli can be seen (yes). The *colors* in the images *in the upper row* represent the difference in the observed response between the target stimuli and nontarget stimuli. The greater the difference, the more the region is colored *red-orange*. Below, averaging overall responses for the other three stimuli (nontargets no, stop, go; in *green*) and for all responses to target stimuli (yes; in *brown*) is shown (Adapted from [118])

region. An increase in the SMR, or synchronization, occurs following the execution of a movement and during relaxation [121]. The advantage here is that these components do not require the actual execution of the movement but solely the kinesthetic mental imagery of this [122]. However, it is not possible to use more than two commands, the increase to three or more leading to a decrease in the classification accuracy. In healthy subjects, many BCIs have shown satisfying results in producing words based on visual [25] and auditory [26] input. The lowest frequencies of signals generated by the cortex and recorded at the scalp are the SCPs. The negative SCPs are usually associated with movements and other functions that involve cortical activation, while positive SCPs are usually associated with a reduction in cortical activity [27]. This system is also limited to two (or less) commands. It has been shown that it is possible to teach participants to control their brain activity (i.e., the SCPs) to move an object on a screen [28]. Using SMRs, Neuper and colleagues [123] have trained a paralyzed patient to use a language support program (LSP, [124]) in order to communicate. The spelling involved the selection of a letter in

successive steps using a virtual keyboard. A predefined set of letters was divided into two subsets and presented at the top and at the bottom of the screen. The patient was instructed to select one of this subset by either relaxing or by using motor imagery. When the patient had selected the subset containing the target letter, this subset was itself divided into two parts, and this until the patient selected the target letter. After several months, the patient was able to control the keyboard with an accuracy of 70%. Another study showed the possibility for a patient with ALS to use a keyboard by the control of SMRs [125].

SMRs have been well studied for BCI and have inspired some approaches for patients with DOC. Goldfine and colleagues [126] recorded EEG from three patients showing command-following at the bedside, while they were asked to perform in motor imagery and spatial navigation imagery. If all patients demonstrated the capacity to generate mental imagery on the same tasks on independent fMRI studies, two of them also showed evidence of modulation of EEG activity during the imagery tasks.

In a further study from Cruse et al., motor imagery tasks were investigated in a cohort of 16 UWS [127] and then in 23 MCS patients [128]. Findings suggested that about 20% were able to voluntary control their brain activity in response to a command ("imagine squeezing your right hand" versus "imagine moving all your toes"). The methodology used in this latter study raised the challenge of assessing patient with DOC. Indeed, in this study, blocks of trials (15 beeps following an instruction) were used in order to decrease the cognitive load associated with the tasks. However, if the use of blocks is usually not an issue in healthy volunteers who present relatively stable EEG over time, it can be a problem in noncommunicative or noncollaborative patients showing nonstationarities in the signal (e.g., vigilance fluctuation or important motor artifacts). Indeed, those patients are more likely to present changes in the EEG which could influence trials and blocks dependencies, leading to a misestimation of the results. This emphasizes the need for appropriate statistical tests and paradigms for that kind of BCI application in severely brain-injured population, as well as the necessity for reanalysis of data using different methods [129, 130]. The paradigm was then improved to decrease the working memory load and circumvent the block design issue. In this paradigm, each trial is started with one of the three instructions (i.e., "Try to move your right hand," "Try to move your left hand," and "And now, relax") that are presented auditorily in a randomized order. The utility of the method as a diagnostic tool has been reported in a single patient diagnosed as being clinically diagnosed in an UWS [131].

Finally, using a combination of different EEG responses for assessing DOC has been recently suggested by Pan and colleagues [132]. In this study, the subject's own face and an unfamiliar face were randomly displayed on the left and right side of a computer screen. The left and right images were flickering at different frequencies, whereas the two image frames also flashed in a random order, eliciting both SSVEP and P3 responses. The LIS patient and 28% of the patient with DOC were able to selectively attend to their own or the unfamiliar image, supporting the idea that hybrid BCI systems could be used as a supplemental bedside tool to detect awareness in patients with DOC.

Invasive BCI

So far, we have presented BCIs using noninvasive systems. As many systems are based on EEG signals measured on the scalp, the quality of recordings is relatively low (distorted signal and low amplitude), the spatial resolution is limited, and training is necessary. Therefore, some studies have focused on invasive recording methods. Recordings are performed either directly at the neuronal level [133–136] or on the brain surface in the case of an electrocorticographic recording [137–139]. BCIs based on intracortical microelectrodes can directly record the activity of neurons and provide a stronger signal. These allow users to control devices such as computer cursors more quickly and accurately [139]. While this technique has not been tested in healthy subjects, participants with ALS showed good performances in the context of complex communication with continuous point-and-click control [140].

Conclusion and Perspectives

The role and potential utility of the EEG have greatly evolved in the last years. The interpretation of the EEG trace is not anymore limited to acute patients and for the monitoring of epileptic activity. Long-term EEG or repeated evaluations are recommended and have shown their importance for diagnostic and prognostic estimation (e.g., EEG reactivity and the presence of sleep patterns). If visual analysis was suggested to provide sufficient information, it can be very time-consuming for clinicians. The development of automated EEG analysis tools should make it more feasible in clinical setting.

The exogenous evoked potentials can also give useful information as regards the patient's prognosis (e.g., N20) and remnant stimulus processing. Their absence is often associated with a bad prognosis. Active cognitive evoked potentials have the potential to improve the detection of signs of consciousness such as response to command in behaviorally unresponsive patients. The active protocols should, however, be standardized and tested on extensive cohort. Besides evoked potentials, active protocols, inspired by BCI research, have been developed based on several sensory modalities. These could be used to improve the clinical diagnosis as it has already been suggested by fMRI and EEG studies. However, the typical vigilance fluctuation observed in DOC patients is a major confounding factor for these applications [141]. Many patients have been evaluated, and only a few have shown signs of consciousness with these paradigms, including patients showing signs of consciousness at the bedside. Further research is needed to clarify whether this is due to a lack of awareness in some patients, the cognitive load associated with the paradigms, the presence of vigilance fluctuation [142], sensory impairments, or the analysis method used. In the future, it is also important to develop systems that are reliable and easy to use in the everyday life. New algorithms should include the automatic detection of artifacts, the single-trial classification, and the possibility to classify a session without training sessions.

In conclusion, EEG represents a very useful tool for the assessment of acute and chronic DOC patients. The information gathered with the EEG should be combined with behavioral and neuroimaging evaluations to improve the prognosis and diagnosis of the patients.

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