PART 1

Fields of Application

1

Brain–Computer Interfaces in Disorders of Consciousness

1.1. Introduction

The notion of an altered state of consciousness describes a large spectrum of pathological states in which the patient is not able to interact with his or her environment by means of speech or gesture. Even if there remain active residual cognitive processes, or if the patient retains some degree of self or environmental awareness, he or she is unable to communicate. These minimal fragments of consciousness can pass unobserved clinically due to motor deficits, sensory disorders, fatigability, cognitive disorders or fluctuations in wakefulness. Caring for patients with altered states of consciousness presents challenges at multiple different levels, not just ethical, but practical, human, and economical, affecting everything from diagnosis to treatment-related decision making. Today, research on altered states of consciousness is a dynamic field of neuroscience with the two-part objective of shedding light on poorly understood neural mechanisms of consciousness, and finding ways to assess patients' levels of consciousness or even restore basic communication whenever possible.

The purpose of this chapter is to provide a brief overview of studies in electrophysiology and neuroimaging that represent advances in terms of both

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care for patients with altered states of consciousness and the way that we view these patients, followed by a presentation of the most recent works performed in this field together with a future outlook based on brain–computer interface (BCI) techniques. In the first section, we show how resting brain signals and passive responses to stimuli can provide the basis for a hierarchical approach to the functional assessment of patients, from the prognosis of coma awakening to the differential diagnosis between different levels of consciousness. In the second section, we present paradigms for eliciting voluntary participation from the patient. The goal of these so-called "active" paradigms is to determine the patient's level of consciousness, as well as his or her capacity to cooperate. Finally, in the third section, we show how the ability to measure brain function in real time could soon make it possible to monitor patients' cognitive functions for diagnostic purposes, restore some form of communication with certain patients and perhaps even assist in their rehabilitation.

1.2. Altered states of consciousness: etiologies and clinical features

1.2.1. *From coma to awakening*

Coma is defined as a severe disorder of consciousness with full loss of awareness and the incapacity to respond to external prompts. Coma occurs following significant brain lesions that are usually the result of traumatic brain injury or cerebral anoxia, but may also arise from other origins such as metabolic, infectious or toxic disorders. Coma is characterized by functional alterations to attention and wakefulness mechanisms in the ascending reticular formation [ZEM 97]. Both the ability to wake (arousal) and the substance of consciousness (awareness) are lost. This acute phase of coma may last from several days to several weeks, during which the future progression of the coma is difficult to predict. If a patient survives the acute phase of the coma, he/she enters a phase in which the eyes are open with the appearance of wakefulness, but with no communication. If no objective signs of a reaction to stimuli are observed, the patient is said to be in a vegetative state (VS, or "unresponsive wakefulness syndrome", see [LAU 10]). In some cases, this VS can last for months or even years – this state is given the name of permanent vegetative state (see [LAU 04]). If the patient is able to follow simple commands or shows purposeful non-reflex behavior, the state is

described as a minimally conscious state (MCS, see [GIA 02]). MCS can refer to a wide range of situations, depending on the nature and the extent of the observed responses. For this reason, some authors distinguish between MCS+ for patients with responses said to be high level (e.g. intelligible verbalization) and MCS- for patients with only low-level responses (e.g. localization of a pain stimulus) [BRU 11].

In the best-case scenario after awakening from coma, the patient recovers to a fully conscious state, with variable degrees of long-term functional consequences. The potential to improve relational capabilities and the timescales of these improvements vary strongly from patient to patient. They are in particular strongly linked to the etiology of the coma. The clinical progression of traumatic comas is generally more favorable than that of anoxic comas, with a faster and stronger recovery of consciousness. One very specific and infrequent postcoma state is locked-in syndrome (LIS, see [BAU 79]), which arises as a result of lesions on the brainstem. This is not a consciousness disorder, as patients awaken from coma fully conscious, but with full paralysis in all voluntary muscles except for the eyelids. Patients' cognitive abilities generally remain intact, but their means of communication are extremely limited, or even non-existent (complete locked-in). Degenerative neurological diseases such as amyotrophic lateral sclerosis (ALS) can also lead to a LIS after paralysis develops progressively in the patient's muscles without affecting his/her consciousness [HAY 03].

1.2.2. *The importance of differential diagnosis*

In a postcoma state, wakefulness is restored but the capacity to interact with others, self-awareness and awareness of surroundings might remain affected to a greater or lesser extent. The patient's state can be thought of as part of a continuum of states of consciousness ranging from fully non-responsive (VS) to a regular state of consciousness (LIS), with MCSs in between.

Establishing a differential diagnosis between VS and MCS, or in other words discerning the presence of some conscious awareness in patients unable to communicate, is particularly crucial. The right diagnosis is the first step toward the right course of treatment. An optimal regime of care should involve interacting with the patient whenever possible, for both basic everyday life situations and consequence-heavy decision making. Clinical

assessment involves observing the patient's spontaneous behavior as well as behavioral changes in response to various stimuli. The goal is to detect a motor response consistent with the given command, an oriented response to sound or pain, an intelligible verbalization or visual tracking or fixation, all of which are signs of emerging consciousness. The differential diagnosis between VS and MCS is somewhat unreliable, as it is difficult to distinguish subtle indications of consciousness from purely automatic responses, and because of the limitations posed by the patient's state. It has been estimated that up to 43% of patients with disorders of consciousness may have been incorrectly diagnosed as vegetative [SCH 09]. Indeed, these patients can suffer from peripheral or cortical sensory deficits, neuromuscular deficits and other pathological conditions that disguise their state of consciousness. Assessment is repeated multiple times to account for possible fluctuations in wakefulness. Carefully structured scoring tests have been validated in an attempt to standardize this clinical evaluation process. One commonly used test is the Coma Recovery Scale Revised [GIA 04, SEE 10], which explores the patient's auditive, visual, motor and oromotor/verbal capacities in depth, as well as communication and wakefulness. The application of these kinds of test should improve the precision of the diagnostic process, but due to the difficulties described above, a standard measure of consciousness does not exist.

1.3. Functional assessment of patients with altered states of consciousness (passive paradigms)

1.3.1. *Prognosis of coma outcome*

For therapeutic, ethical and economical reasons, establishing a prognosis for both survival and awakening during the acute phase of coma is the most urgent medical objective. The prognosis depends on the etiology of the coma, the severity and extent of brain lesions, and the patient's clinical functional state. The criterion used to evaluate prognostic techniques is the clinical outcome of the patient 6 months or 1 year after coma onset. Classically, patient states after coma are evaluated according to the Glasgow Outcome Scale [JEN 75], which originally comprised three levels of awakening (no disability, moderate or severe disability), VS and death. This system has the benefit of being simple, but although it may be used to describe the functional state and overall level of dependency of the patient, it does not provide further

information about potential intermediate disorders of consciousness such as MCSs [GIA 02].

1.3.1.1. *A multimodal approach in search of objective criteria*

For many years, the prognosis of coma was based on a collection of clinical observations and tests performed with anatomical neuroimaging and electrophysiology. The techniques applied in routine clinical procedures are particularly effective at predicting the most unfavorable developments (persistent coma or death). The most commonly used methods in the context of clinical assessment during the acute phase are the pupillary light reflex and the Glasgow Coma Scale [TEA 74, YOU 09]. The latter is based on ocular, verbal and motor responses. A patient who does not open his/her eyes and neither responds nor produces a motor response is given the minimum score of 3. A healthy, conscious subject receives a score of 15. Anatomical neuroimaging (by X-rays, computed tomography scan or by magnetic resonance imaging (MRI)) has excellent spatial resolution. It allows the localization and severity of cortical lesions to be assessed and any damage to the basal ganglia to be detected [YOU 09, GRE 14]. Diffusion MRI (diffusion-tensor imaging, (DTI)), a biomarker of the severity of damage to white matter bundles, was recently used to successfully establish a prognosis for traumatic [GAL 12] and anoxic comas [LUY 12].

1.3.1.2. *The essential role of electrophysiology*

Electrophysiology offers excellent temporal resolution, which facilitates an approach to the patient's functional state [GUE 10]. It is non-invasive and inexpensive, and can be applied directly at the patient's bedside by means of scalp electrodes. The electrophysiological tests routinely applied with comatose patients are resting electroencephalograms (EEG) and evoked potentials (EPs).

Resting EEG is an indicator of cortical electrical activity. Its visual inspection is commonly used in intensive care units to identify typical scenarios with unfavorable prognosis ("malignant" EEGs, which include isoelectric patterns, strongly discontinuous patterns, patterns with periodic epileptic graphoelements and patterns with stationary slow waves indicating defective thalamocortical coupling). Conversely, signs of a good prognosis include EEG traces that are only slightly slowed, with graphoelements indicative of sleep, fluctuating over time and/or reactive to auditory or

nociceptive stimuli. However, there is a wide range of intermediate situations in which visual inspection is not very informative for the prognosis.

EPs characterize modifications in electric brain activity in response to sensory stimuli. As they have very low amplitude relative to background EEG, EPs are identified by averaging the signals over repeated stimuli. Components are characterized by their poststimulus latency. Early latencies indicate sensory processing at subcortical and cortical levels. Cognitive processes evoke later responses and are referred to as event-related potentials (ERPs). Somatosensory cortical responses (somatosensory EPs (SEPs), approximately 30 ms after stimulus onset), and to a lesser extent short-latency brainstem auditory evoked responses (BAEPs, within 10 ms poststimulus) and middle-latency primary cortical auditory responses (MLAEPs, within 100 ms) are interpreted as strongly predictive of unfavorable developments when absent. Hence, in axonic comas, SEPs are used to identify patients prone to high mortality rate and possibly guide a decision to limit active therapeutics [MAD 96]. Traumatic comas are less black-and-white. An observed absence of SEPs may still be compatible with favorable developments, particularly in children [JAV 12]. Focal lesions can modify these cortical potentials without endangering vital processes. Conversely, the presence of SEP and/or MLAEP components in a coma does not guarantee that consciousness will recover [LOG 03].

1.3.1.3. *The benefit of event-related potentials*

For over 20 years, the absence of primary sensory EPs (in particular, SEPs) in comas has been used to predict unfavorable developments. More recently, interest has grown in "cognitive" EPs with later latencies (ERPs) in comatose patients, with the expectation that they might prove useful for predicting favorable outcomes [LEW 06, MOR 14]. Auditory paradigms with more sophisticated stimuli than the simple clicks used for BAEPs and MLAEPs evoke responses that reflect the successive cortical stages of information processing. One commonly employed paradigm is the "oddball" paradigm, which supplies repeated (standard) sounds that are occasionally randomly replaced by other (deviant) sounds. This paradigm appeals to both the encoding of acoustic input in the auditory cortex, indexed by the fronto-central N1 sensory response around 100 ms [NÄÄ 87], and an automatic mechanism for detecting the violation of an established pattern, indexed by the mismatch negativity (MMN). The MMN appears around

120 ms and has generators in the auditory and frontal cortices [NAA 78, GIA 90]. Its presence during coma is a very specific marker of awakening [KAN 93, KAN 96, FIS 99, FIS 04, FIS 06]. In postcoma states, it is a strong marker of improvement [KOT 05, WIJ 07]. Finally, the infrequent occurrence of an unexpected stimulus in an *oddball* paradigm triggers attention orienting, characterized by the *novelty* P3 component between 250 and 300 ms [FRI 01]. Moreover, calling the patient's first name among other simple sounds triggers a particularly robust *novelty* P3. The detection of this wave during coma is strongly correlated with awakening 3 months after coma onset [FIS 08].

1.3.2. *Functional patterns in postcoma states*

Experimental study of conscious perception in healthy subjects has shown that it is associated with the activation of large networks of interconnected brain areas [ZEM 01]. A number of studies in neuroimaging and electrophysiology have explored brain function in postcoma states, and have attempted to identify functional patterns that might be used to distinguish patients diagnosed as minimally conscious (MCS) from patients with no signs of consciousness (VS).

Positron emission tomography (PET) had previously shown that glucose metabolism is globally diminished in patients in a VS as compared to healthy subjects [BEU 03], with particular deficits in corticocortical and thalamocortical connectivity [LAU 99]. DTI shows significant differences between VS and MCS in white matter, in the subcortex and the thalamus [FER 12]. In VS patients, auditory or pain stimuli only activate the sensory cortices, as observed with PET [LAU 00, LAU 02] and functional MRI (fMRI) [DI 07], whereas MCS patients exhibit stronger connectivity between secondary auditory regions and temporal and frontal associative cortices, as observed with PET [BOL 04, BOL 05]. An fMRI study on 41 patients showed that hierarchically assessing speech processing, from low-level hearing to high-level comprehension, is beneficial for both diagnosis and prognosis [COL 09]. The activation of the default mode network by means of personal questions is stronger in MCS than in VS patients [QIN 10, HUA 14]. The deactivation of this network after stimulation is thought to indicate the interruption of introspective processes. It was found to be reduced in MCS patients and absent in VS patients [CRO 11].

Recent quantitative methods enable the assessment of the frequency content of resting EEG and its fluctuations in time and space. In group studies, these methods succeeded in differentiating vegetative from MCS patients (see [LEH 12b] for a review). Disordered states of consciousness are associated with slowed basic rhythms. VS compared to MCS patients show an increase in the lowest frequencies (1–4 Hz delta band) and a decrease in the alpha band (8–12 Hz) [LEH 12a, SIT 14, FIN 12]. Patients' behavioral assessments are strongly negative correlated with brain signal complexity, which can be identified by various measures of entropy [SIT 14, GOS 11, WU 11]. A reduction in brain connectivity, as evaluated by different approaches, is more strongly apparent in VS than MCS patients [LEH 12a, KIN 13]. Effective connectivity may also be observed with transcranial magnetic stimulation (TMS) in combination with high-density EEG. The perturbational complexity index was recently suggested as a measure of complexity of brain responses to TMS perturbations in order to evaluate a patient's level of consciousness [CAS 13].

For EPs, we saw earlier that the presence of an MMN in response to deviant stimuli indicates the preservation (or recovery) of elementary automatic processes and is a predictor of a potentially favorable outcome. However, MMN alone is not sufficient to assess patients' consciousness [MOR 14]. A more in-depth exploration based on realistic generative models of the neural dynamics underlying these evoked responses ("dynamic causal modeling") compared the effective connectivity of VS and MCS patients, and control subjects, showing disruptions to top-down connections (from frontal to temporal cortex) in the group of vegetative patients [BOL 11]. Event-related potentials with higher latencies, in particular the P300 and N400 components, have also been tested with the objective of detecting residual cognitive functions in patients with altered states of consciousness. The P300 (or P3, around 300 ms after stimulus onset) can be evoked by infrequent stimuli. It contains at least two subcomponents, the frontocentral P3a associated with involuntary detection processes, and the parietal P3b associated with attention-related differentiation [POL 07]. The P3b is the typical signature of attention-related processing when the deviant stimulus is designated as the target, but it can also arise without instructions when the deviant stimulus is particularly infrequent and noticeable, or is associated with some special meaning [FRI 01]. In healthy subjects, calling the subject's first name triggers a P3, both while awake and while asleep,

when presented as part of a series of other names [PER 99] or simple sounds [HOL 06, EIC 12, EIC 13]. When presented in a series of simple sounds, it triggers a *novelty* P3, which indicates attention orienting. We saw earlier that the presence of this wave during a coma is a good indicator of favorable outcome [FIS 08]. In some patients with persistent disorders of consciousness, it was observed but did not correlate with the level of consciousness established by behavioral assessment [FIS 10]. When spoken together with other first names, the subject's first name triggers semantic recognition processes and evokes an augmented P3 that has been observed primarily in patients with minimal states of consciousness and patients with LIS, but which has also been observed in some VSs [PER 06]. The N400 is evoked by words (read or heard) inconsistent with their semantic context (word out of place in a sentence, pairs of non-matching words), while awake [KUT 00] and asleep [PER 02]. This response was observed in patients with minimal states of consciousness, but also in patients thought to be in a VS [KOT 05, SCH 04]. A recent study investigated the response to words presented in semantically matching and non-matching pairs to a group of patients (15 VS and 15 MCS) [ROH 15]. The study was able to distinguish a response resembling a N400 in both groups, and a more delayed parietal positivity in the MCS group only, suggesting that the N400 might represent an unconscious response to semantic violations, whereas delayed parietal positivity might represent conscious processes. Both of the two components were difficult to detect on an individual level, even in healthy, conscious subjects. Still, it is interesting to note that the three patients in which they were successfully identified were minimally conscious, and that two of them subsequently regained consciousness.

Long-latency potentials (P3 and N400) are indicative of cognitive processes that are activated without explicitly demanding the patient's attention. These potentials appear as false positives when the clinical behavioral assessment is considered as the ground truth. The existence of these false positives highlights the ambiguity of the results. On the one hand, we know that clinical observations tend to underestimate the level of consciousness of some patients. On the other hand, while the mechanisms underlying these responses have been studied in depth in healthy subjects, they are less known in patients with disorders of consciousness. For example, a recent study based on oscillatory responses to out-of-place words showed

that these words had a specific effect on MCS patients that was absent in VS patients but distinct from the effect observed in healthy subjects [SCH 11].

The neuroimaging and electrophysiology tests presented above observe the brain in a resting state or in response to stimuli. They allow the functional state of the patients' brain to be evaluated and are capable of detecting cognitive functions that are more or less intact. Their validity as a clinical tool for assessing the patient's individual level of consciousness depends on both the reliability of the reference diagnosis based on clinical observations, and our understanding of conscious perception in healthy subjects.

1.4. Advanced approaches to assessing consciousness (active paradigms)

"Can you hear me?" Only an explicit answer from the patient would prove that he/she has heard and understood the question, and therefore is conscious. If the patient is unable to answer by behavioral means, his/her cerebral responses may be observed instead. These responses should be voluntary, and not the result of a reflex. They need to unambiguously prove that the patient is deliberately participating in the task and has understood the instructions. To this effect, recent studies have attempted to implement "active" paradigms in patients with disorders of consciousness, with the goal of evaluating their level of consciousness. The general idea is to compare two conditions corresponding to two different mental tasks. Motor imagery tasks and stimulus-counting tasks have been suggested. Neuroimaging (fMRI) and electrophysiology (EEG and ERPs) techniques have been applied in this context.

The first demonstration was provided by Owen *et al.* in a vegetative patient 5 months after severe head trauma [OWE 06]. The patient was asked to consecutively perform two mental imagery tasks, including one motor (playing tennis) and one spatial (moving from room to room within her house). fMRI showed persistent and distinct response patterns to each instruction during the 30 s of the task, similar to those observed individually in healthy subjects [BOL 07]. The patient had therefore understood the stated instructions and had responded. This result was reproduced in five patients (four VS and one MCS) among 54 (23 VS and 31 MCS) in a multicentric study [MON 10]. It should be noted that in two out of the four VS diagnosed

patients who managed to willfully modulate their brain activity, additional clinical tests ultimately revealed evidence of consciousness that had previously been missed. Subsequently in one patient, answers to yes/no questions were successfully obtained by using the cerebral responses to the same tasks (tennis/spatial navigation) as a binary code. So far, classical forms of bedside communication had not been possible with this patient. A variant of the fMRI motor imagery task was tested more recently on a small group of patients [BAR 11, BAR 12]. The patients were instructed to alternate between imagining themselves swimming and resting. In 14 healthy subjects, blood oxygen level dependent responses in the supplementary motor area were successfully used to identify periods when the subject was performing the task and to answer binary or multiple-choice questions [BAR 11]. The results obtained in six of the patients highlight the dissociation between the results of motor imagery and behavioral assessments. They also show the utility of extending the analysis to the whole brain, rather than simply focusing on motor regions [BAR 12]. Indeed, cortical reorganization can occur in patients with severe traumatic lesions.

Motor mental imagery can also modulate EEG power in the *mu* (7–13 Hz) and *beta* (13–30 Hz) bands over motor regions (see Chapter 4 of Volume 1), In five control subjects and three patients, modulations of the EEG between 4 and 24 Hz were compared during a motor task (swimming), spatial navigation task (moving through the house) and resting. One MCS and one LIS patient managed to modulate their EEG, proving that they were performing the task, but these modulations were different from those observed in healthy subjects [GOL 11]. Another team performed the study with the instructions: "each time that you hear the sound, imagine clenching your right fist, then relax" and "imagine wiggling your toes, then relax". One initial study considered 16 patients diagnosed as vegetative. Three patients modulated their EEG consistently in response to instructions [CRU 11]. In a second study with 23 MCS patients, five did perform the task [CRU 12a]. The etiology of the coma appears to play an important role: the comas of the five patients able to perform the task were traumatic in origin. The results of the eight patients with other etiologies were all negative [CRU 12a]. A simplified version of this paradigm was successfully tested in a patient who had been in a VS for 12 years [CRU 12b]. Only four electrodes were used, and the instructions ("move your right/left hand", "relax") were often repeated in order to reduce the required mental effort. This simple 20-min EEG

procedure, which managed to elicit willful responses from patients unable to communicate, could potentially be used routinely in clinics to assess consciousness.

Another way of revealing the capability of a patient to cooperate is to draw his/her attention to designated target stimuli among other stimuli. For instance, counting target stimuli involves components of attention and working memory that are believed to play key roles in conscious processes [ZEM 05]. In terms of event-related potentials, the response to target stimuli exhibits a parietal P3 [POL 07]. In another study, the stimulation paradigm was arranged as eight randomly presented names, including the patient's name [SCH 08]. During two phases of active listening, patients had to count the number of occurrences of a given name, or of their own name. The results were analyzed in groups of subjects (eight VS, 14 MCS and 12 control subjects) and individually. Like control subjects but unlike VS patients, MCS patients exhibited augmented P3 waves in response to target stimuli, suggesting willful participation in the counting task. This effect occurred later in the patients compared to the control subjects. On an individual level, the results were more nuanced, with only nine MCS patients producing significant responses to targets, in at least one of the active tasks. This poor result might be due to fatigue, or fluctuations in awareness, and the authors suggest that the recordings should be repeated to avoid false negatives [SCH 08].

A new oddball paradigm (given the name of "local-global" by its authors) allows two mechanisms elicited by the violation of a sequential rule to be highlighted [BEK 09]. The first mechanism identifies violations that are close in time, and is based on short-term sensory memory. It occurs automatically and is represented by the MMN. The second mechanism detects violations of the global structure of the sequence, further apart in time and therefore inaccessible to sensory memory. It requires the preceding stimuli to be actively maintained in working memory, and is represented by the P300 wave. In practice, the "local-global" paradigm is composed of successive chains of five brief stimuli, the first four of which are always identical. When the final stimulus breaks the pattern of the previous four, an MMN is evoked, whether or not the subject is paying attention to the stimuli ("local effect"). In each block, all consecutive chains are identical, except for 20% of them (deviant chains). In healthy subjects, a P3 is expected to be evoked by these "global" deviant chains when they are explicitly recognized and counted. However, if the subject's attention is engaged in a visual task, the chains that violate the

global rule are not consciously perceived, and do not evoke a P3. When counting, this "global effect", which activates a large brain network as revealed with fMRI, is considered by the authors to be a neural signature of conscious processing. The "local-global" paradigm was initially tested with eight patients (four VS and four MCS). An automatic "local" effect was obtained in all patients, except for one VS patient. A conscious "global" effect (P3) was only observed in three MCS patients [BEK 09]. In a group of 22 patients diagnosed as vegetative, two patients responded positively to the "global" test. These two patients showed objective signs of consciousness 3 or 4 days later [FAU 11]. The specificity of the global effect as a measure of consciousness was confirmed by means of a series of 65 recordings performed in 49 coma and postcoma patients with varying etiologies [FAU 12]. The global effect was observed in seven of the 13 patients diagnosed as conscious, and in four of the 28 MCS patients. The poor sensitivity of the test (only 11 patients were responsive in the group of 41 non-vegetative patients) might be due to the fact that the test is highly demanding in terms of cognitive resources.

In summary, on the one hand, active paradigms confirm that some patients may be incorrectly identified as vegetative by clinical assessment; on the other hand, they require cognitive performances that may be out of reach of some conscious patients due to cognitive deficits inherently associated with the patients' lesions or temporary factors (level of wakefulness during the test). Determining the clinical validity of these tests is made difficult by the lack of a reference diagnosis [CRU 14].

An appropriate assessment of patients' brain functions should involve hierarchical sensory and cognitive tests followed by active paradigms, if possible repeated, so that patients who are able and willing to communicate by BCI may be accurately identified.

1.5. Toward the real-time use of functional markers

Active paradigms discussed in the previous section all rely on the willful modulation of brain activity, following a set of given instructions. Repeating this test makes it possible to establish with statistical significance whether the instructions were properly followed or not. This procedure can be used to establish that the patient is awake and conscious [OWE 06]. It can also serve

as a tool for communication, allowing yes/no questions to be answered [MON 10].

1.5.1. *Real-time approaches to communication*

Thus, active paradigms possess all the ingredients of a BCI, except that they do not operate in real time. In this context, the purpose of a BCI would be to provide an operational tool, as simple and practical as possible, that may be used at the patient's bedside [LUA 15]. This is why the most commonly preferred technique is once again EEG [CRU 11]. Of course, similarly to other applications of BCI, the goal is to establish a line of communication (decode a response online) on the basis of a small number of signals, which are usually noisy. Several types of signals have already been explored in attempts to communicate with patients with disorders of consciousness. In this section, we will give three recent examples.

1.5.1.1. *Attention-related modulation of evoked auditory responses*

Lule *et al*. tested an auditory BCI based on the P300 wave and the principles of the *oddball* paradigm [LUL 13]. Sixteen control subjects and 18 patients were tested, of which two had been diagnosed with LIS, 13 with MCS and three with VS. After asking a question, four stimuli "yes", "no", "stop" and "go" were repeated in a cycle. The patients and subjects were asked to concentrate on the "yes" or "no", depending on the desired response. The target response was expected to produce a P300-type wave. A classifier was operated in real time to provide feedback informing the user of the selected answer. The BCI was calibrated prior to being used. Online, the control group achieved an average performance of 73% correct answers. One LIS patient achieved 60%, whereas none of the MCS or VS patients were able to communicate. An offline analysis made it possible to improve the performance of healthy subjects and of the two LIS patients, but on average no significant improvement was observed in the MCS and VS patients.

In a relatively similar study performed with 14 healthy subjects and two patients with ALS, Hill *et al*. showed that using words directly associated with the subject of the instruction (answer "yes" or "no") was more effective than using standard sounds such as beeps [HIL 14]. The performance achieved was around 77% of correct answers, both in the healthy subjects and the ALS patients. Note that both of these patients were still capable of

communicating by other means, and that one of them was familiar with the usage of a visual BCI.

1.5.1.2. *Mental motor imagery*

Mental motor imagery is known for producing characteristic brain activity (desynchronization of the *mu* and *beta* frequency bands) in a way that is relatively similar to the activity produced when executing an actual movement [PFU 99]. Each effector's electrophysiological response has its own scalp topography when put into motion, whether mentally or physically, which may be used to distinguish a number of different commands, typically between 2 and 4 (see Chapter 4 of Volume 1). In general, these approaches require an initial calibration phase and voluntary participation from the user, similar to BCIs that use EPs.

The study by Cruse *et al*. mentioned above [CRU 11] was one of the pioneering studies in this field. Since then, two other studies, one offline and the other online, have continued to explore this kind of strategy.

The first study compared two relatively complex mental imagery tasks (doing sport and navigating through a familiar environment) with the task of attempting to move the feet and the task of performing passive movements with the feet (movements executed by the intervention of a third party) [HOR 14]. Six MCS patients participated in three recording sessions each. Although each task led at least once to classification results above chance level, these results could not be reproduced from session to session, and success rate varied from 64% to 80% for distinguishing between four different tasks.

With only three EEG sensors, the second study compared two tasks of mental motor imagery, one with the right hand, and one with the toes, in four MCS patients [COY 15]. Over several sessions, this study used an original approach to explore the impact of visual and auditory feedback on the online BCI performance, at least in three of the patients. Although no improvement over time could be proven, the performances, which were subject to strong fluctuations, sometimes significantly exceeded chance levels.

1.5.1.3. *Visual frequency markers*

A third well-known category of BCI that has recently been explored for communicating with patients with LIS or disorders of consciousness is the

category of visual frequency markers (SSVEP, see Chapter 4 of Volume 1). This marking system is based on the repetition of a visual stimulus at a given frequency. The successive responses evoked by these stimuli produce a strong signal at the same frequency as the stimuli. This signal is known to be amplified when attention is focused on one such stream of stimuli.

One study recently tested a BCI with two commands, independent of the direction in which the subject is looking, based instead on the direction in which the subject's attention is focused, either toward yellow stimuli flashing at a frequency of 10 Hz, or at red stimuli flashing at a frequency of 14 Hz [LES 14]. The experiment showed that the absence of information associated with the direction in which the subject is looking led to a decrease in performance when distinguishing between the two options. Still, an online application of this interface allowed eight of 12 healthy subjects to answer yes/no questions with an average accuracy of 80%. By contrast, only one of the four LIS patients managed to communicate at a level significantly better than chance.

Finally, another study chose a hybrid visual paradigm, combining the principle of frequency markers with a P300-based approach. The objective was again to test the performance of a channel for binary communication in healthy subjects ($n = 4$), one LIS patient, but also MCS ($n = 3$) and VS ($n = 4$) patients [PAN 14]. The stimuli consisted of two pictures of faces presented simultaneously on screen, but flashing at different frequencies (6 and 7.5 Hz, respectively). One of the faces was unknown, whereas the other was the face of the BCI user. Moreover, a P300 wave could be generated by randomly and infrequently displaying a frame around the image. The dominant direction of the attentional focus in response to an explicit instruction was estimated by the combined analysis of two different types of EEG responses. While the four subjects in the control group achieved performance varying between 82% and 100%, the LIS patient achieved from 72% to 78%. Only one VS patient and one MCS patient achieved performance above chance level, namely between 66% and 78%.

1.5.2. *The benefit of BCIs in disorders of consciousness for purposes other than communication*

BCI technology now makes it possible to analyze brain activity in real time and provide feedback to the user. This allows us to imagine ways of

providing means of communication to patients who are otherwise incapable of producing reproducible and interpretable voluntary actions. But the analysis of brain signals in real time can have other applications in the context of disorders of consciousness. We shall name three such applications.

First of all, real-time analysis of the resting EEG can supply markers associated with wakefulness, awareness and complexity [SIT 14], which can contribute to the diagnostic process, and additionally serve to indicate the opportune moment for testing an active paradigm or a BCI for communication.

In the context of customized medical care, real-time signal analysis, in particular of EEG, could also help to optimize the diagnosis and prognosis of VS and MCS patients. Indeed, beyond simply detecting evoked responses such as the MMN and the P300, measuring the modulations of these waves by voluntary (focusing the attention) or implicit (learning the frequency of a deviant sound) processes [LEC 15] could provide a more finely tuned and objective assessment. To achieve this, recent studies suggest that computational models of these evoked responses [OST 12, LIE 13] combined with a real-time approach could allow passive test protocols to be optimized for each individual [SAN 14].

Finally, BCIs pave the way for true closed-loop paradigms, in which the objective of sensory feedback is to facilitate the recovery of consciousness, or at the very least to improve functional markers. This would potentially be achieved over the course of a large number of sessions similar to neurofeedback protocols (see Chapter 13 of Volume 1).

1.6. Conclusion and future outlook

The clinical assessment of patients with disorders of consciousness is slowly integrating electrophysiological measures such as the analysis of resting EEG, and early-latency EPs, middle-latency EPs and other cognitive potentials such as MMN and P3. These measures have improved the process of establishing a prognosis for patients. Furthermore, more detailed and rigorous behavioral assessments have demonstrated uncertainties in the diagnostic process. Our primary objective remains to equip ourselves with objective measurement tools that will allow the functional state of patients to be assessed as precisely and reliably as possible. The studies reviewed in this

chapter show that no single technique exists that can achieve this goal perfectly. Instead, a multimodal approach is now the preferred method for compiling a body of evidence containing behavioral, structural, functional, metabolic and electrophysiological information.

Just over 10 years ago, fMRI confirmed that relying on clinical assessment alone can cause diagnostic errors, showing that patients thought to be in VSs were potentially capable of responding to instructions by producing certain types of brain activity in a voluntary and reproducible manner [OWE 06]. The fallout of this study and its replications [MON 10] was spectacular, opening a new avenue of research with the goal of communicating with patients incapable of performing actions that can be interpreted as conscious. Paradoxically, it was fMRI, a technique that is seldom employed for BCIs, that set these events in motion. fMRI provides excellent spatial resolution. However, it is inconvenient, extremely limited in its use with this category of patients, and very expensive. For these reasons, subsequent research naturally turned toward less expensive and more practical bedside alternatives such as electrophysiology. A few initial studies have also considered the potential of functional near infrared spectroscopy [SOR 09].

BCIs appear to be the only alternative for overcoming the current limitations in assessing and communicating with these patients, and applications in this area are still in their infancy, with a vast amount of potential yet to be unlocked. Still, the first studies have highlighted the difficulty of the endeavor. BCIs that were implemented for simple, binary communication did not achieve the desired accuracy rate of 100% correct classification, even in healthy subjects. Also, when working with patients the performance is drastically reduced, yet the absence of a significant performance level cannot be interpreted as the absence of consciousness or of the capacity to respond [PET 15]. Today, we can say with relative certainty that any progress in the assessment of these patients will necessarily involve a combination of techniques, requiring repeated measures, or perhaps an optimized choice of when to perform optimized measurements, and the adaptation of BCI paradigms to suit each patient as best as possible [KÜB 14].

The most recent research in this area has shown that the best experimental protocols for revealing intact cognitive processes in patients remain to be discovered, which might potentially involve exploring the personal and

emotional aspects of cognition. fMRI has recently shown that decoding techniques can be used to evaluate the perception of the emotional content of a film or a story [NAC 15]. With EEG, playing the patient's favorite music tracks before electrophysiological assessment could potentially allow the responses evoked by sounds in an *oddball* paradigm to be more easily detected [CAS 15].

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