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REPORT ON STATE-OF-THE-ART OF METHODS TO STUDY CONSCIOUSNESS INCLUDING BCI AND INTERACTION OF EEG/FMRI/FNIRS – MEDICAL PERSPECTIVE

Principal contributor named in the grant

Medical Research Council, Cognition and Brain Sciences Unit, Cambridge, UK

Optional contributions from:

University of Würzburg, Germany

University of Tübingen, Germany

Maastricht University, Netherlands

Abstract

This document is the report for deliverable 4.2 of the DECODER project. BCI technologies have had widely different implementations, depending on the technique used for the measurement of brain activity, encompassing invasive and non-invasive technologies (Gerven et al., 2009). We discuss here the non-invasive technologies (fMRI, FNIRS, EEG) that have been applied, or can be applied to non-responsive patients. These BCI applications are rapidly developing, but face specific challenges, stemming from the nature of the 'non-responsive' state. We discuss how the non-responsive state constrains BCI applications, and review separately each of the three main non-invasive technologies.

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1 Introduction

1.1 BCI systems

Recent years have seen an explosion of interest in applying advances in cognitive neuroscience to developing brain-computer interface (BCI) systems (Kübler & Kotchoubey, 2007). BCI technology measures brain activity and uses it for several types of interventions, including regulation of the user's brain activity with neuro-feedback, non-motoric control of the physical environment and communication with the external world. A fully-fledged BCI system involves a closed cycle from sensory stimulation and task performance, to the measurement and analysis of the resulting brain signal, to the outputting of a desired function, and, finally to the feeding back of the relevant information to the person undergoing BCI procedure (Gerven et al., 2009, Kübler & Kotchoubey, 2007). This cycle can be repeated iteratively until the desired result is achieved (Gerven et al., 2009).

This review focuses on BCI research that can be applied to aid communication with behaviorally non-responsive patients, or patients who are not able to produce any form of consistent behavioral output. Before delving into the BCI applications aimed at communication with behaviorally non-responsive patients, we note another, major strand of BCI research, which involves learning to voluntarily regulate one owns' brain activity via neuro-feedback (Weiskopf, Scharnowski et al., 2004). This important strand of BCI research aims to understand and develop treatments for particular pathological conditions (deCharms, 2007, 2008; Sitaram et al., 2007; Weiskopf, Scharnowski et al., 2004; Weiskopf et al., 2007;), including chronic pain (deCharms et al., 2005), and possibly to enhance cognitive functioning in healthy humans (Rota et al., 2009). However, because it relies on training of the person undergoing the BCI procedure, it cannot be applied in its current state to non-responsive patients. For this reason, we do not discuss this research further in this review (see Abarbanel, 1995 for an in-depth review of neurofeedback; Sitaram et al., 2009 for fMRI-based neurofeedback studies).

BCI technologies have had widely different implementations, depending on the technique used for the measurement of brain activity, encompassing invasive (ECoG, ME, MEA) and non-invasive technologies (fMRI, FNIRS, EEG) (Gerven et al., 2009). We discuss here the non-invasive technologies (fMRI, FNIRS, EEG) that have been applied, or can be applied to non-responsive patients. These BCI applications are rapidly developing (see e.g., the TOBI project), but face specific challenges, stemming from the nature of the 'non-responsive' state. In the following sections we describe briefly the non-responsive state, and how it constrains BCI applications. Subsequently, we review separately each of the three main non-invasive technologies.

1.2 Non-responsive patients

The term 'non-responsive' is used to label patients who do not show any behavioral signs of command following, or willful behavioral response to repeated clinical examinations (The Multi-Society Task Force on PVS, 1994; Jennett & Plum 1972). However, as recent studies have shown (Owen et al., 2006; Monti et al., 2010), behaviorally non-responsive patients can demonstrate responses to commands, by willfully modulating their brain activity. Hence, the lack of behavioral response does not necessarily imply that the patient does not process the incoming requests for communication, or that he or she cannot initiate a response. BCI can enable *behaviorally* non-responsive patients to communicate through their brain activity thus overcoming their behavioral limitation.

Non-responsive patients are a heterogeneous group that encompasses patients with different disease etiologies, and varying degrees of brain damage and cognitive impairment. Patients labeled as non-responsive can have a range of conditions from disorders of consciousness (DOC), including the vegetative state (VS) and the minimally conscious state (MCS), to the locked-in syndrome (LIS). We discuss these different types of conditions briefly below.

Patients suffering from DOC can be severely impaired. Most VS and MCS patients have suffered some degree of brain-damage through a variety of conditions, including traumatic brain injury, anoxic brain injury, meningitis, brain-stem stroke, etc (Multi-Society Task Force on PVS, 1994), which will have impacted their cognitive capacities.

The diagnosis of the vegetative state is based on the lack of a sustained, reproducible, purposeful, or voluntary behavioral response to sensory stimulation (visual, auditory, tactile, or noxious) on repeated examinations (Jennett & Plum 1972; The Multi-Society Task Force on PVS, 1994; Royal College of Physicians of London, 2003; Laureys, 2005). Central to the clinical description of the VS condition is what is termed as 'wakefulness without awareness' (Jennett & Plum, 1972). VS patients show clear signs of wakefulness, but no awareness of themselves and of the environment.

The diagnosis of "minimally conscious state" was recently added to the spectrum of DOC (Giacino, 2002) to characterize a subgroup of DOC patients, who show intermittent signs of awareness, which although inconsistent are reproducible, and differentiate these patients from those in the vegetative state. Despite the fact that MCS patients can show the ability to follow commands, due to their highly fluctuating levels of awareness, they remain unable to establish any functional communication. MCS patients may be misdiagnosed as VS, in cases where behavioral signs of conscious awareness are repeatedly missing at the time of assessment (Owen & Coleman, 2008; Monti et al., 2009).

Overall, the clinical assessment of DOC patients is extremely difficult and relies heavily on the subjective interpretation of observed behavior. Brain-damaged patients experience fluctuations of vigilance, which may mean that they meet the criteria for consciousness at one point in time, but not others (Kübler & Kotchoubey, 2007). The fluctuation in the patient's state coupled with the subjective nature of the assessment, and, often, an inadequate experience and knowledge on the part of the assessor, due to the relative rarity of these conditions, leads to a high rate of a misdiagnosis of VS (up to 43%) (Andrews et al., 1996; Schnakers et al., 2009).

Another group of non-responsive patients, those diagnosed as 'locked-in' syndrome (LIS), are thought to have largely preserved sensory, cognitive, emotional abilities (e.g., Schnakers et al., 2008; Lulé et al., 2010). Acute LIS is commonly caused by stroke, specifically by small, circumscribed bilateral ventro-pontine lesions in the brainsteam, when an (almost) complete motor de-efferentiation can lead to quadriparesis or quadriplegia and anarthria (Plum & Posner, 1966). However, sometime consciousness may be impaired (Pantke, 1999; Tavalaro & Tayson, 1998), especially if there is brain swelling beyond the eareas imediately affected by the infarct, or where there are additional extrapontine (e.g., thalamic) infarcts (Kübler & Kotchoubey, 2007).

The LIS can occur in varying degrees of severity. Patients suffering from the so-called *classical* LIS are immobilized throughout their body, but retain blinking and small vertical eye movements. Patients suffering from the *complete* (or, *total*) LIS (CLIS) cannot perform any voluntary movement, including motor responses and eye movements (Bauer et al., 1979). Because of their inability to produce covert behavior, CLIS patients are often misdiagnosed as lacking conscious awareness (Leon-Carrion et al., 2002).

A complete lack of motor functions similar to CLIS is sometimes observed in other patients, such as those suffering advanced stages amyotropic lateral schlerosis (ALS) (Birbaumer et al., 1999; Bruno et al., 2008; Kübler and Birbaumer 2008). The lack of motor functions in these patients can also lead to an incorrect diagnosis of vegetative state. Thus, the misdiagnosis of CLIS and ALS patients contribute to the high rate of misdiagnosis in the VS patients.

1.3 Further considerations

The expression „BCI for disorders of consciousness (DoC)“ appears paradoxical. This is due to a cliché which moves around from one article to another one, a story about two different types of disorders. On the one hand, according to the cliché, there is a locked-in syndrome (LiS) characterized by intact consciousness but a complete (or almost complete) motor paralysis. On the other hand, there is a persistent vegetative state (PVS), a condition in which any kind of conscious awareness is completely lost but motor functions are preserved albeit impaired. Adjacent to PVS (in which no indication of consciousness can be obtained) there is a minimally conscious state (MCS) in which a patient can show weak and inconsistent signs of conscious awareness.

According to this view, there is *essentially* nothing common between the LiS, on the one hand, and PVS and MCS, on the other hand. They can only *appear* similar, but in fact they are rather opposite, according to the above definition. From this point of view there cannot be any BCI for DoC but only one for patients who falsely appear to have a DoC. The aim of a BCI researcher is, therefore, the development of assessment techniques which goes beyond the superficial similarity and separates the sheep who are fully conscious but paralyzed and can use a BCI, from the goats who don’t have any chance (see King James Bible, Mt. 25, 33 ff.).

However, there are many reasons of why the story about the two apparently similar but inherently opposite kinds of disorders is wrong. To begin with the LiS, the progress of the intensive care in the last two decades resulted in many LiS patients survived and to some degree restored their functions. A number of them remembered their worst condition (Bauby, 1997; Hübner, 1995; Pantke, 1999; Tavalaro, 1998), and all of those who wrote such reports complained of various disorders of consciousness (from inability to concentrate to massive hallucinations and memory loss) at least in the acute phase of the decease.

The reasons for this are both neurophysiological and functional. On the one hand, a LiS patient may be fully conscious but (almost) completely paralyzed if the lesion (as a rule, a consequence of a stroke in the basilar artery) is *exactly* restricted to the anterior portion of the pons cerebri. Unfortunately the nature is not always concerned by the interests of scientists; the infarct region is frequently extended backwards to the reticular formation, upwards to the sensory pathways or sidewards to the cerebellar peduncles (Al Sardar & Grabau, 2002; Chia, 1991; Latronico et al., 1993; Park, Sohn, & Kim, 1997; Patterson & Grabois, 1986). All of this can lead to disorders of perception, attention, wakefulness and memory. The fact that most LiS patients have at least partially disturbed auditory or somatosensory evoked potentials (Bassetti, Mathis, & Hess, 1994; Benitez, Ernstoff, Wang, & Arsenault, 1994; Chia, 1991; Gütling, Isenmann, & Wichmann, 1996; Towle, Maselli, Bernstein, & Spire, 1989; Facco, Caputo, Fiore, & Giron, 1989; Landi, Fornezza, DeLuca, Marchi, & Colombo, 1994) obviously contradicts to the view that LiS is a pure motor disorder. In the acute phase an oedema of a broader region is involved in addition to the main infarct, and this temporary lesion can even be more dangerous than the primary pontine cell death due to the local anoxia (Krieger et al., 1993; Onofrj, Melchionda, Thomas, & Fulgente, 1996). Moreover, some LiS patients described in the literature had additional destructive processes outside the bridge region (Chia, 1984; Latronico, Antonini, Taricco, Vignolo, & Candiani, 2000).

However, even if there is no morphological defect which might lead to disorders of cognition and consciousness, functional pathophysiological mechanisms can result in a similar pattern. Sudden fallout of the entire information about the position, forces and torques in muscles, joints and tendons is a catastrophe for the brain. Apart of the classical pontine LiS, a similar condition can result from inflammatory and degenerative diseases of the nervous system, such as amyotrophic lateral sclerosis (ALS) (Durrleman & Alperovitch, 1989; Hayashi & Kato, 1989; Hayashi & Oppenheimer, 2003; Kübler et al., 2001). Also these diseases can be related to serious cognitive, in addition to motor, deficits. ALS is characterized by severe neuronal degeneration in the primary motor cortex and the anterior horn of the spinal cord. In a less degree, however, degenerative processes are recorded in the prefrontal cortex and subcortical nuclei as well, which can underlie severe cognitive deficits up to dementia (Ludolph et al., 1992; Kato, Hayashi, & Yagishita, 1993; Kato, Oda, Hayashi, Kawata, & Shimizu, 1994; Strong, Grace, Orange, & Leeper, 1996).

Now let us turn to the other pole, i.e., PVS and MCS. There is some evidence that they can hardly be conceived of as separate typological entities. Rather, the diagnostic notion MCS (Giacino et al., 2002; Giacino & Kalman, 1997) has been introduced to mask the uncertainty of the physicians and to replace an unattractive term "questionable PVS" (Bernat, 2002; Shewmon, 2002). According to Jennett (Jennett, 2002), the diagnosis PVS should be restricted to the patients in which no slightest sign on any kind of conscious awareness or subjective experience can be found. However, numerous philosophers from Husserl to Searle and neuroscientist from Edelman (Edelman, 2001) to Damasio (Damasio, 1999) share the common intuition that there are "low-level" kinds of conscious awareness such as simple experience of pleasure/non-pleasure whose clinical diagnosis may be very difficult because this low-level consciousness, in contrast to our common reflexive awareness, does not possess language.

But the situation is even worse. Whereas the classical view, described in neurological textbooks, clearly distinguished between the neuromorphology of the LiS (as already said, typically a lesion in the anterior bridge) and that of PVS and MCS (cortical or thalamic destruction, or a diffuse axonal injury), there is evidence now, that LiS symptoms can also develop in patients with typical PVS neuropathology. PVS (or MVS) and LiS are, therefore, not mutually exclusive; rather, LiS can emerge on a certain stage of the reconvalescence from PVS through MCS (and through LiS) to some more benign rest condition.

1.4 Cognition in non-responsive patients

In the following sections we focus on BCI applications for patients diagnosed as VS, as this label groups patients rendered non-responsive due to a variety of medical conditions and cognitive abilities. Although a clinical diagnosis of vegetative state implies lack of cognition, this is not necessarily the case. The heterogeneous disease etiologies and disease progression in patients diagnosed as VS leads to varying degrees of cognitive capacities in this patient group. Recent research challenges the current diagnostic criteria for detecting consciousness, which are based on the patient's ability to communicate their awareness through a recognized behavioral response.

In particular, EEG and fMRI studies that have used passive (Kotchoubey et al., 2005; Menon et al., 1998) and active paradigms (Owen et al., 2006; Monti et al., 2010) have indicated that VS patients can process stimuli of varying complexity, including word meanings (Coleman et al., 2007, Coleman, Davis et al., 2009). Further, Monti et al (2010) showed that a patient diagnosed as VS could communicate by answering the experimenter's questions with 100% accuracy, by willful modulation of his brain activity. This finding suggests that behavioral measures may be too coarse to determine the presence of conscious awareness in some DOC patients. If the patient's ability to produce a behavioral response is lost, but conscious awareness remains, functional neuroimaging and EEG can provide a more sensitive measure to assessing the patient's awareness and spared cognitive abilities (Owen et al., 2006; Owen & Coleman, 2008; Laureys et al., 2004; Monti et al., 2010).

1.5 Challenges for BCI applications for non-responsive patients

fMRI-based BCI applications can help to test for signs of conscious awareness, and attempt communication with behaviorally non-responsive patients. However, applications of BCI for non-responsive patients are amongst the most challenging.

The main hurdle in communicating with behaviorally 'non-responsive' patients is that, unlike for healthy participants, where the BCI user's intent is clear (e.g., to regulate own brain activity via neuro-feedback), no inferences can be drawn, including whether or not there is any intact sensory processing, conscious awareness, spared cognitive capacities, and or, communicative intent on the part of the patient. This limitation dictates the need for a multimodal hierarchical assessment of the patient's cognitive capacities as a necessary precursory step to adapting a particular BCI technique. Consequently, DECODER has adopted exactly this approach.

In general, BCI systems must be as simple as possible to facilitate the patient's response, and must not rely on extensive training. Further, depending on the patient, they may be restricted by the type of sensory modality in which the stimulus can be presented (e.g., audition). VS patients most often lack the ability to fixate, or display visual pursuit, traits that are part and parcel of the definition of the vegetative state in some countries, for example in the United States (Multi-Society Task Force on PVS, 1994). Impaired visual processing, limits severely the type of BCI application that can be used in these patients (but, see Martin et al., submitted). Consequently, BCIs that rely on auditory and somatosensory stimulation are being developed (auditory: e.g., Kübler et al., 2009, Halder et al., 2009; article in Frontiers in Neurosprosthetics 2010 on tactile P300).

2 Measurement technologies used in BCI

2.1 Invasive and non-invasive BCI technologies

BCI applications encompass a wide range of measurement methods from invasive to non-invasive technologies (Gerven et al., 2009). Invasive technologies, e.g., electrocorticogram (ECoG), single-electrodes (ME), or electrode arrays (MEA), which involve implantation of electrodes in the cortex, have superior signal to noise-ratio, and better detection of high-frequency oscillatory activity than non-invasive technologies (Leuthard et al., 2004; Ramsey et al 2006, Miller et al., 2007, Schalk et al., 2008). Although invasive technologies can obtain very high performance, they can only be used in rare circumstances, and have to our best knowledge not been applied to non-responsive patients to date (see Hill et al, 2006). For this reason, we focus on non-invasive BCI applications that use EEG, fMRI and fNIRS. Below we review each of these technologies in turn.

2.2 fMRI-BCI

BCI applications for non-responsive patients that are based on hemodynamic measurements (fMRI, fNIRS) are still in a nascent state. Hence, most BCI research discussed in this section involves communication strategies, rather than fully-fledged communication systems, in the sense of the canonical definition of BCI systems (Kübler & Kotchoubey, 2007; Gerven et al., 2009). For example, current applications do not involve bi-directional feedback between the experimenter and the patient.

fMRI measures changes in blood flow and oxygenation (known as hemodynamics) that are linked to neural activity (Ogawa et al., 1993; Kwong et al., 1992). The hemodynamic measure of brain activity can be transformed into discrete units of information to be used in BCI. The strengths of fMRI for BCI applications are its non-invasive nature, global brain coverage, including the cortex and deep, sub-cortical structures, and the excellent spatial resolution of specific brains structures (millimeter range). Recent advances in *real-time* fMRI (Cox et al., 1995), or online analysis and interpretation of the fMRI signal, have increased the appeal of this technology for BCI applications (deCharms, 2008). The limited temporal resolution of fMRI (seconds range), may or may not be a problem, given that optimal practical spatial or temporal scale for reading brain states remains unknown (deCharms, 2008). In applications that require decision-making and command following, which may involve a delay from stimuli processing to response, especially in the case of brain-damaged patients, a seconds' range temporal resolution may be adequate. Among the weaknesses of fMRI are its cost and lack of portability, shortcomings that may be mitigated by another hemodynamic technology, fNIRS. (See fNIRS section).

In the following sections we discuss existing fMRI BCI techniques developed for non-responsive patients, or that have the potential to be applied to this patient group. Several aspects of the hemodynamic signal have been used for such BCI applications. A widespread approach has involved using the precise localization of distinct brain regions involved in different cognitive functions. More specifically, different mental imagery tasks (e.g., playing tennis, navigation, mental calculation, etc.) activate distinct brain regions, and therefore can be used to generate different and discrete responses, that can be transformed into information units (Monti et al., 2010; Yoo et al., 2004; Lee, Ryu et al., 2009). Another approach has involved quantifying the strength of the hemodynamic response at discrete levels (e.g., low, middle, high), and using it to convey discrete information units (Goebel et al., 2004, 2005; Dahmen et al., 2008). More recently, the timing of the hemodynamic response has also been used to separate different types of responses that are systematically time-lagged one from the other (Sorger et al., 2009).

2.2.1 Hierarchical assessment with fMRI

There is growing consensus that BCI techniques especially those for non-responsive patients should be based on prior hierarchical assessment of cognitive function (Owen et al., 2005; Owen & Coleman, 2008; Kübler and Kotchoubey, 2007).

The Cambridge team has developed an fMRI-based multimodal (visual and auditory) hierarchical assessment battery for non-responsive patients (Coleman, Bekinschtein et al., 2009). The battery is administered subsequent to the standardized behavioral assessment scales (CRS-R: Giacino et al., 2004) and electro-physiological (EEG) assessments, which test the integrity of basic sensory processes and warrant further investigation with fMRI. The hierarchical battery tests neural processing at increasing levels of complexity from sensory responses to those which require higher-level cognition and volition, such as semantics or attention selection.

2.2.2 Visual modality

The visual hierarchical assessment battery (Monti et al., submitted) tests the presence of predicted responses to increasingly more complex visual stimuli through five presentation steps. The first five steps involve passive paradigms, whereas the final one involves an active paradigm that tests the patient's volition, or the ability to willfully modulate his/her brain activity. The first step tests low-level visual responses, by comparing brain activity due to simple visual stimuli, e.g., flashing checkerboard, to activity during fixation. The second step tests the response to colour, by comparing activity due to coloured Mondrian patterns with activity due to monochrome patterns. The third tests responses to visual motion, by comparing activity due to moving squares with activity due to static squares. The fourth tests object-selective responses, by comparing activity due to visual objects with that due to scrambled versions of those objects. The fifth step tests responses to specific object types, such as faces and houses, which may be especially salient for the human brain (Kanwisher et al., 1997; Epstein & Kanwisher, 1998). Finally, the last step tests whether the patient can demonstrate volition. The patient is asked to pay attention to one of two overlapping objects, either to the house or to the face. Differences between the 'attend-house' and 'attend-face' conditions are investigated, to determine whether the patient can chose to selectively attend to one of the two images.

Although VS patients have fluctuating levels of wakefulness, involving long periods of eye closure (Owen & Coleman, 2008), hierarchical assessment of visual function is possible in some DOC patients even when they demonstrate no ability to fixate in tests performed at the bedside (see Monti et al., submitted).

2.2.3 Auditory modality

Following a similar principle, the auditory hierarchical assessment battery tests the presence of predicted responses to increasingly more complex auditory stimuli. The auditory battery is composed of 3 presentation steps. The first step tests the presence of responses to low-level auditory stimuli by comparing brain activity due to sounds with activity during silence. The second step tests speech perception, by comparing activity due to sentences with activity due to signal correlated noise. The final step tests speech comprehension and semantic processing by comparing activity due to high ambiguity sentences with activity due to low-ambiguity sentences (Coleman et al., 2007; Coleman, Davis et al., 2009).

2.2.4 Assessing volition

When fMRI activity indicates that the patient retains aspects of speech comprehension, more complex paradigms can be administered to investigate the presence of conscious awareness and to communicate with the patient. Mental imagery paradigms are particularly useful as they require the patient's active participation, and elicit specific brain activity by virtue of the patient's imagination, and in the absence of external stimulation apart for instructions to engage in different imagery tasks.

The presence of voluntary, reliable, and sustained brain activity in response to command as revealed by fMRI can be used as a proxy for voluntary behavior (Owen et al., 2006; Owen & Coleman, 2008; Monti et al., 2010; Monti et al., submitted).

In 2006, Owen and colleagues reported one such task that was used successfully to detect willful modulation of brain activity in the absence of external stimulation in behaviorally non-responsive VS patients. This task was chosen on the basis of prior assessment in 24 healthy participants (Boly et al., 2007). Four different mental imagery tasks were pretested to select a simple yet robust paradigm that could detect brain activity reliably for each individual patient. These were: spatial navigation, sub-vocalization, face imagery, and motor imagery (Boly et al., 2007). Among this set, the motor imagery and spatial navigation tasks produced the most robust activity and reliable activation, with the least inter-subject variability in the location of brain activity for each participant (Boly et al., 2007). The motor imagery task produced robust activity in the supplementary motor area (SMA), whereas the spatial navigation task produced robust activity in the bilateral parahippocampal gyri, in a region known as the Parahippocampal Place Area (PPA), in the posterior parietal cortex (PPC), and in the lateral pre-motor cortex (PMC) (Boly et al., 2007). These regions have been associated with performing motor actions (Yoo & Jolesz, 2002) and scene perception or spatial navigation (Weiskopf, Mathiak et al., 2004), respectively (Weiskopf, Scharnowski et al., 2004). Based on these findings, a dual task paradigm involving motor and spatial imagery was used in VS patients (Owen et al., 2006).

2.2.5 Volitional Paradigms

Owen and colleagues used this volition paradigm to address two questions. First, they tested the presence of conscious awareness in non-responsive patients (Owen et al., 2006). They asked whether a patient who shows no behavioral response, could show signs of conscious awareness through willful modulation of task-specific brain activity in response of the experimenter's command (Owen et al., 2006). They tested a female patient, who at the time of the study had been unresponsive for 5 months, and had been clinically diagnosed as VS (Owen et al., 2006). In addition, they tested 16 healthy participants as controls. In the motor imagery task, participants were asked to imagine plying tennis (for 30s) when they heard the command "tennis", and to relax (for 30s) when they hear the command "relax." In the spatial imagery task, they were asked to imagine moving around the rooms of their homes, when they heard the command "house" and to relax when they hear the command "relax". The task was presented in a classic box design (on–off; 30 s each). In total, a patient is asked to perform each 'on' and 'off' task five times over a 5-min scan period.

In response to these instructions, the VS patient showed task-specific fMRI activity in the respective predicted regions for each task (Owen et al., 2006). When instructed to imagine playing tennis, the patient produced brain activity in the SMA regions, whereas when instructed to navigate around her house, she produced activity in the PPA, PPC, and PMC regions. The patient's activity was indistinguishable from the healthy participants's brain activity in these regions (Owen et al., 2006).

The patient's brain activity was robust, reproducible, task-specific, and sustained over long time-intervals (30s) at a time. This result suggested that the patient comprehended the instructions and correctly responded to the commands by performing voluntary brain activity in the absence of overt action. This indicated beyond any doubt that the patient was aware at the time of the scanning. Indeed, the patient went on to recover within 6 months of the study's publication. This study indicated that fMRI can be a powerful tool for detecting conscious awareness in patients that are diagnosed as vegetative state. Therefore, these findings have implications for subsequent care and rehabilitation, as well as for legal and ethical decision making (see also D1.2) for these patients. More recently this approach has been validated in EEG, where a VS patient has been found to elicit the same pattern of brain activity during motor imagery, as a locked-in patient and a healthy participant (Cruise et al., 2010).

In subsequent work, Owen and colleagues asked whether a patient, who shows signs of conscious awareness, can communicate his or her thoughts merely by willful modulation of his/her brain activity?

Monti et al (2010) used a similar paradigm to establish communication with patients who showed signs of conscious awareness, despite a clinical diagnosis of vegetative state. The suitability of this volitional paradigm for communication was initially validated in healthy participants. Monti and colleagues (2008) asked participants to respond 'yes/no' to simple autobiographical questions, by selectively imagining to play tennis, or to navigate the rooms in their homes, depending on the answer. They were able to decode the answers in all 16 healthy participants with 100% accuracy, after only 5 minutes of scanning, on the basis of answer-specific selective fMRI activity (Monti et al., 2008).

Following on from this result in healthy participants, Monti et al (2010) applied this technique successfully to communicate with a patient who held a clinical diagnosis of vegetative state for 3.5 years prior to the study (Monti et al., 2010).

Monti et al (2010) tested 54 patients with severe brain injury, including 23 diagnosed as VS and 31 diagnosed as MCS, and 16 healthy controls. Initially, two localizer scanning sessions were conducted where all participants (controls and patients) were asked to perform the motor (tennis playing) and spatial (house navigation) imagery. The fMRI activity in the SMA and PPA, neural regions expected to activate for each task respectively, was investigated. The tasks used the same box-car design as the one used in Owen et al (2006) and summarized above.

After these initial scans, the 16 control participants, and one VS patient who showed the most reliable activity during the two motor imagery tasks, underwent fMRI communication sessions, where they attempted to answer yes-or-no questions. They were instructed to respond during the imagery session by using one type of mental imagery for "yes", and the other for "no". Participants were asked to respond by thinking of whichever imagery corresponded to the answer that they wanted to convey. Communication scanning was identical to the localizer scanning with the exception that the same neutral word "answer" (instead of "tennis"/"house") was used to cue each response to a question, and the word "relax" to cue the rest periods. To decode the answer, each communication scan was compared to the two localizer scans and a similarity matrix (based on Euclidian distance) was used to determine which task/answer the participant had performed; it was then determined whether that was the factually correct answer to the question. The investigators did not know the answers prior to judging the fMRI data.

First, four patients diagnosed as VS showed willful, task-specific, and sustained (30s) modulation of their brain activity in the expected regions of interest, SMA and PPA for the tennis and house navigation task, respectively. The patients' brain activity pattern for the two tasks, closely matched the pattern observed in the healthy participants, and indicated that they were aware, understood the commands and responded to them in the required way. This was consistent with the previous finding from Owen et al (2006), and suggested that fMRI can detect signs of residual and cognitive function in the absence of covert behaviour.

Second, the answers provided by the healthy controls, were decoded 100% accuracy. Strikingly, the VS patient, was also able to provide answers to 5 questions that were decoded with 100% accuracy on the basis if the fMRI activity alone. It was not possible to evaluate the answer to a 6th question posed to the patient, as there was insufficient fMRI activity in the regions of interest. This groundbreaking result showed that fMRI can establish a patient's ability to communicate solely by modulating the brain activity. By contrast, this ability could not be established at the bedside despite thorough clinical assessment (Monti et al., 2010).

In 49 of the 54 patients no significant changes to the fMRI activity was observed in the imagery tasks. These negative findings could have been due to deficits in language comprehension, decision making, working memory or executive function. It is also possible that incomplete task performance would have yielded brain activity too weak to be observed with this paradigm. Alternatively, some patients may have been unconscious (permanently or transiently) during the scanning and not participated at all in the task (Monti et al., 2010). It is not possible to determine in these patients why the expected brain activation was not observed (Monti et al., 2010). The multiplicity of interrelated viable explanations for this finding, highlights the difficulty of communicating with non-responsive patients. It is possible that future developments of more sophisticated assessment methods, e.g., adaptive testing of cognitive functions (Iversen et al., 2008) will help to develop BCI for an increasing number of patients.

2.2.6 fMRI BCI work in healthy participants

Below we discuss BCI techniques tested in healthy or in partially responsive participants, but which have potential applicability for non-responsive patients.

Yoo et al (2004) showed that healthy participants could navigate through a simple two-dimensional maze by controlling their thoughts. Participants were instructed to use four different mental imagery tasks ('right hand motor imagery', 'left hand motor imagery', 'mental calculation', and 'inner speech') to generate different cursor commands (e.g., ''right,'' ''left,'' ''up,'' and ''down''). Lee and colleagues demonstrated that simple movements of a robotic arm could be generated and controlled by using the same principles (Lee, Ryu et al., 2009). Although these studies were carried out in healthy participants, rather than non-responsive patients, they indicate the potential of mental imagery paradigms for generating several discrete states that can be dissociated with fMRI, and used as distinct commands in BCI applications. However, the applicability of this paradigm for non-responsive patients would face several limitations. A critical limitation is that this paradigm relies on visual processing, a capacity that is commonly compromised in VS patients. A more important limitation is the reliance on short-term memory capacity. Patients are required to remember several response options at any time. Given that healthy short-term memory capacity has a limitation of around four items (Cowan, 2001; Mitchell, 2009) (depending on individual variation), this memory requirement may be significantly strenuous for brain-damaged patients, and as a result, highly error prone.

Another fMRI approach has aimed at developing BCI techniques for communicating with LIS patients. Goebel and colleagues have used the strength of the fMRI signal, rather than its spatial pattern, to encode discrete information units for use in BCI applications. For example, participants used neuro-feedback to adjust their brain activity strength to three target levels (''low,'' ''middle,'' and ''high''), within the same fMRI session (Sorger et al., 2004), or to four levels, when training was extended to four fMRI sessions (Dahmen et al., 2008). Further, this group showed that by using different levels of brain signal strength, participants could play an analog of the computer game 'pong' (Goebel et al., 2004, 2005). Similarly to the studies reviewed above (Yoo et al., 2004; Lee, Ryu et al 2009), the applicability of this paradigm for non-responsive patients would face several limitations. In addition to the aforementioned potential issues (e.g., reliance on visual processing), this paradigm makes use of extensive training. As discussed above, extensive training is not possible with patients diagnosed to be in a vegetative state, at least at an initial stage, when no information on the patient's cognitive abilities beyond the clinical diagnosis is available.

Another BCI technique tested in healthy participants, but aimed at LIS patients has exploited the temporal onset and offset of the BOLD signal at the level of individual trials to encode information. In a study with healthy participants, Sorger et al (2009) were able to generate differential BOLD responses necessary to answer a four-choice question within the length of a single trial (1 minute). A dynamic visual display guided the answer encoding. To indicate their choice, participants had the option of one of two tasks, performed at one of four moments in time indicated by a highlighted letter on the screen, offset by 5 seconds one from the other. Thus, the BOLD responses could be differentiated with respect to at least two of three features of the BOLD signal, its source location, onset, and offset. After the answer encoding, an automated decoding procedure deciphered the answer by analyzing the generated single-trial BOLD responses online. Participants' answers were decoded correctly with a mean accuracy of 94.9%, ranging from 75% to 100% (Sorger et al., 2009).

This study makes an important contribution by demonstrating that single-trial fMRI time-courses can be used as a robust source of information. Further, it shows that fMRI can be used to communicate multiple-choice answers online/in real time and within a reasonable time-scale (e.g., 1min). This length of time would be patient-friendly, and not introduce excessive time pressures. However, similarly to the studies discussed above the applicability of this design for communication with non-responsive patients would be limited by its reliance on extensive training, and visual processing.

2.2.7 Summary of fMRI-BCI applications

In summary, studies with non-responsive patients show that the distinct spatial patterns of the fMRI activity elicited by different mental imagery tasks can be used to detect conscious awareness in patients that appear non-responsive at the bedside (Owen et al., 2006; Monti et al., 2010). Willful, task-specific, reproducible and sustained brain activity produced in response to experimenter's instructions can be used as a proxy of voluntary behavior in non-responsive patients (Monti & Owen, in press). This willful modulation of brain activity can be used to generate discrete information units of information that can be used unequivocally communicate with these patients via questions requiring simple “yes” or “no” answers (Monti et al., 2010). Further, studies with healthy participants show that it is possible to dissociate multiple (4) response options either based on the spatial pattern of the fMRI signal (Yoo et al., 2004; Lee, Ryu et al., 2009), or on discrete levels of BOLD signal strength, which can be modulated via neuro-feedback (Goebel et al., 2004; 2005; Dahmen et al., 2008). Moreover, Sorger et al (2009) show that the temporal onset and offset of the fMRI activity can be used to communicate (encode and decode) multiple (4) response options in real-time, in the duration of a 1 minute long trial. Although this research has been carried out in healthy participants it suggests interesting BCI techniques that may be applicable to non-responsive patients with modifications.

2.2.8 Future avenues and challenges for fMRI-BCI

Online fMRI

Time is of essence and rapid communication can make real differences for the patient's health. The efficiency in BCI systems can be improved by the development of online/real-time communication methods.

Using online fMRI methods, a multistage assessment and communication procedure could be performed online, potentially leading to communication with the non-responsive patient within the same scanning session. For example, at an initial stage, the hierarchical assessment of the patient's spared cognitive faculties can be performed rapidly online, enabling the choice of the appropriate volitional BCI paradigm while the patient is lying in the scanner. As a second stage, the BCI technique (e.g., Owen et al., 2006; Monti et al., 2010) could be applied aimed to determine whether the patient shows conscious awareness. If the patient is found to be consciously aware, at a third stage, two-way communication with the patient could be attempted. Rapid, online decoding of patient's answers could be incorporated in a paradigm where the patient's answer inform the experimenter's feedback and so forth, leading to back and forth communication. These developments would pave the way for fully-fledged BCI systems with bi-directional feedback to be used in non-responsive patients.

Multi-voxel pattern analysis (MVPA)

Another development that holds much promise for the improvement of current BCI techniques is increasing the amount of information that can be extracted from the brain activation per unit of time.

In particular, the application of multi voxel pattern analysis (MVPA) methods has the potential to increase amount of information that can be decoded per amount of time. Traditional univariate analyses used in current fMRI BCI techniques average across a brain region, and compare overall changes in fMRI signal strength between different types of conditions (Friston, 1995). They discard information contained in the signal pattern across voxels, which can accurately discriminate between different types of stimuli (Haxby et al., 2001). By contrast, MVPA uses the pattern of the fMRI response to dissociate overlapping neural pattern to different stimuli or mental states, which would otherwise be difficult to disentangle with traditional univariate methods (Haynes & Rees, 2006).

Recently MVPA has been used to decode the identity of items from memory, or mental states driven by the participant's intention, in the absence of external stimuli (deCharms, 2007). For example, recent studies have shown that the identity of an imagined object can be decoded with high accuracy based on the fMRI response pattern in visual cortex (Reddy et al., 2010). Thus, MVPA has the potential to dissociate several mental states/responses elicited by a single command in a simple, single-task paradigm, in contrast to most current work which classifies brain activity into limited number of response options per command (Kay et al., 2008; Chadwick et al., 2010). For example, by using an MVPA method it may be possible to ask the participant to patient to express how much pain he/she feels on a sliding scale form 1-10 by imagining the right number. If the MVPA method can accurately classify the answer, this would give 10 response options to a simple command. The participant does not have to perform different mental imagery tasks for each one of these options.

Further, MVPA methods have already been applied in real-time (LaConte et al 2007; Lee, Marzelli, et al 2009). However, current MVPA methods come with one limitation - a trade-off between classification accuracy and amount of fMRI data. MVPA methods are dependent on the amount of data for their classification, with higher classification accuracies for larger amounts fMRI data. This may be a problem for patients where the amount of scanning time is limited by patient's availability, and, further, should be as short as possible to ensure the best performance and avoid fatigue.

Mobility

Another important factor for BCI systems aimed at non-responsive patients, who cannot move freely, is their applicability in diverse settings. High-density NIRS systems (Sitaram et al., 2009) have the potential to provide relatively inexpensive and mobile hemodynamic BCI systems. For example, it may be possible to decode "yes"/"no" answers using a modified version of the volition task discussed above (Owen et al., 2006) with a NIRS system outside the clinic. Such a method would provide a direct, albeit limited, method for the family and carers to communicate with the patient. (see below)

2.3 fNIRS-BCI

As already mentioned above, fNIRS provides a relatively new and (next to fMRI) a second non-invasive possibility to use haemodynamic (metabolic) brain signals as an input modality for BCIs. In the following, the general functional principles of fNIRS (3.1), its *pro*s and *con*s (3.2) as well as the current state-of-the-art (3.3), future avenues and challenges (3.4), and the potential (3.5) of fNIRS-based brain-computer interfacing will be addressed.

2.3.1 General functional principles of fNIRS

FNIRS measures a similar haemodynamic brain response to fMRI (Villringer and Chance, 1997; Irani *et al.*, 2007) and both methods show similar vascular sensitivity (Huppert *et al.*, 2006). As fMRI, fNIRS only *indirectly* measures local brain activation, namely through haemodynamic changes (e.g., of the blood volume, the cerebral blood flow or the concentration of de-/oxygenated haemoglobin) that come along with neuronal activity. Note, however, that the indirect nature of the brain signal does not constitute a disadvantage in the BCI context as here it is only important to have a robust brain signal available which is voluntarily producible and controllable.

In terms of signal acquisition, fMRI and fNIRS methods considerably differ. As the fNIRS technology is still in its early development and has been (compared to fMRI) only rarely used so far, its general functional principles will be summarized in the following.

In the beginning (at about 1985), near-infrared spectroscopy (NIRS) was used only for clinical purposes to observe the level of the oxygen saturation of brain tissue (Kirkpatrick, 1997; Madsen and Secher, 1999; Wardle and Weindling, 1999). Later, since the early 1990s, this optical technology has become an imaging method in fundamental neuroscience that – as *functional* NIRS (fNIRS) – allows for localising brain activation (Sitaram *et al.*, 2009). However, just recently, fNIRS was recognised as a BCI measurement technology (Coyle *et al.*, 2004; Naito *et al.*, 2007; Sitaram *et al.*, 2007).

FNIRS uses the penetrability of biological tissue (e.g., of the cranium or brain tissue) for light from the near-infrared spectrum (700-1000 nm). Apart from the fact that there is always light scattering, so-called “chromophores” (in this case oxygenated and deoxygenated haemoglobin) – differing in their absorption spectra – absorb the light (Fallgatter *et al.*, 2004). From the amount of absorbed near-infrared light of specified wavelengths one can then calculate the concentration of oxygenated and deoxygenated haemoglobin and infer the functional state (‘active’ or ‘non-active’) of the neuronal tissue. However, because of many not accurately controllable influences, the absolute concentrations of the chromophores can not be measured. Therefore the exact brain activation level can not be determined (Fallgatter *et al.*, 2004). Nevertheless, relative changes in the signal time course are sufficient for the localization of brain functions or for use in BCI applications as it does apply to fMRI.

How does measuring fNIRS work practically? At first, light with a particular wavelength of the near-infrared spectrum is produced and sent through flexible electro-optical cables. These cables end up in so-called “optodes” that are mounted on the participant’s head. The light coming out of the emitter channel of these optodes penetrates the subjacent brain tissue and gets absorbed according to the concentration of the chromophores. The not absorbed light is received by light detectors and sent back to the control unit. Then, the concentration values of oxygenated and deoxygenated haemoglobin can be calculated with a spectrophotometric analysis considering the ratio of emitted to reflected light of a certain wavelength. By means of these values, the neuronal activity in the brain tissue directly below the optode-detector pair can be inferred.

In the last years, fNIRS has undergone a substantial technical and methodological development. Recent studies convincingly show that results obtained with this method nearly achieve the accuracy obtained with other data acquisition techniques (Zeff *et al.*, 2007; White *et al.*, 2009). Novel fNIRS systems with many closely placed optode-detector pairs (so-called “high-density” systems) allow for measuring cortical haemodynamics on different brain locations simultaneously. However, also fNIRS systems with fewer channels can be used very efficiently since the optodes and detectors can be placed very flexibly, *i.e.*, the placement can be optimized for each particular case. Nowadays, there are a number of commercial systems available including even wireless systems that allow for free movement up to 30 m outside or 10 m inside of buildings (Atsumori *et al.*, 2007; Atsumori *et al.*, 2009).

2.3.2 Pros and cons of fNIRS

The main advantage of fNIRS is surely that it is portable/mobile and is (as compared to fMRI) less sensitive to (e.g., head) movement artefacts. This makes this technology usable at the patients' bedside (for diagnostic purposes) or even beyond clinical settings in daily-life situations (for alternative communication with non-responsive and 'locked in' patients). Moreover, fNIRS is relatively affordable, less technically demanding, and easier to operate/handle than fMRI. This might allow large patient populations to benefit from fNIRS-based BCI applications in the future. Furthermore, it does not require to expose patients to a high magnetic field, so that paramagnetic medical equipment does not constitute an excluding factor for its use as in the case of fMRI.

Another advantage of fNIRS is that it is nearly noiseless. FMRI, for example, comes along with a sound level of about 80dB. Thus fNIRS can be regarded not only as a completely safe and harmless but also as a relatively comfortable method. Therewith, fNIRS is suited for long-term use in patients, including children. Another advantage of fNIRS constitutes the possibility to combine this technique with other neuroscience methods as fMRI, EEG, and transcranial magnetic stimulation (TMS). This might become beneficial for the further development of this technique – also in the context of BCI research and applications. This opens up, for example, the possibility to develop hybrid BCIs that might prove to be helpful in order to increase BCI accuracy.

While fNIRS has certain benefits against fMRI (see above), it only allows reliably measuring haemodynamic responses in cortical tissue that is close to the head surface (up to approximately 3 cm in depth). Thus, brain activation in, e.g., subcortical structures can not be targeted that would be accessible with fMRI. Moreover, the spatial resolution of fNIRS (in the range of a few cubic centimetres) is considerably lower than the resolution obtained with fMRI (in the range of a few cubic millimetres).

2.3.3 State-of-the-art of fNIRS-based BCIs

To our knowledge, research so far has not been focused on using fNIRS for diagnostic purposes (assessing the state of consciousness) in non-responsive patients but only for the development of BCIs for compensation of lost motor functions (communication and environmental control).

The first related fNIRS study was conducted by Haida et al. (2000). They demonstrated that an ALS patient in a complete 'locked-in' state was able to evoke brain activation as measured with fNIRS a) within the motor cortex by performing motor imagery and b) within Broca's area during a speech-related task. Therewith, Haida and colleagues demonstrated that fNIRS-based BCI systems might be principally used successfully by this patient group.

In the first fNIRS-based BCI study, Coyle et al. (2004) instructed healthy participants to change a visually presented feedback signal (in this case a circle) not only through real but also through imagined hand movements (opening and closing of the right hand). The size of the visual feedback signal altered according to the change of the oxygenation level of the haemoglobin within the contralateral motor cortex. By this study, Coyle and colleagues could demonstrate that motor imagery produces similar (although lower) fNIRS signals to the actual movement. In a follow-up study, the same research group presented an fNIRS-based BCI setup (called 'Mindswitch') – consisting of a single channel, *i.e.*, one optode-detector pair – by which they could generate two commands ("yes"/"no") and therewith provide a basic means for communication (Coyle et al., 2007).

In the same year, Sitaram et al. (2007) demonstrated that by using a 20-channel fNIRS system, imagined and the real finger movements could be differentiated with more than 80% accuracy when comparing the evoked brain activation patterns. Moreover, they proposed an fNIRS-based BCI setup that would in principle allow for (relatively slow) letter spelling. Next to these feasibility studies, the study by Naito and colleagues (2007) using a single-channel fNIRS system is of particular importance – showing that for about 40% of the 17 tested patients in a complete ‘locked-in’ state voluntary control via performing different mental tasks (e.g., ‘mental calculation’ or ‘mental singing’) was possible which enabled the patients to communicate “yes” and “no” answers that could be successfully decoded with 80% accuracy. Before this study, no other kind of BCI (including those based on neuroelectric signals, e.g., EEG) had been successfully applied in completely ‘locked-in’ patients who would benefit most – even substantially – from motor-independent communication means as they do not have any other alternative communication possibilities left. This could signify that haemodynamically based communication techniques might become especially important for this patient group.

In the most recent related fNIRS study, Luu and Chau (2009) proposed a BCI paradigm based on directly decoding neural correlates of decision making (subjective preference evaluation). Healthy participants were asked to mentally evaluate two different drinks and to decide which they preferred while fNIRS signals from the prefrontal cortex were obtained by means of a multi-channel system. Using mean signal amplitudes as features and linear discriminant analysis, the researchers were able to decode which drink was preferred with an average accuracy of 80% on a single-trial basis.

2.3.4 Future avenues and challenges of fNIRS-based BCIs

We consider the abovementioned main limitations of fNIRS (relatively low spatial resolution, restricted depth pervasion) as being not crucial and still acceptable for BCI purposes. Of course, these constraints require a careful exploration of suited passive and active paradigms that evoke differential brain activation patterns within superficial cortex regions (*i.e.*, in crowns of gyri). In this context, it might prove beneficial to exploit in a first step the high resolution of fMRI and to transfer then the gained knowledge to the fNIRS technology. Thus, one idea would be to perform fMRI and fNIRS experiments in the same individuals – possibly even simultaneously.

Moreover, the use of multi-channel (so-called “high-density”) fNIRS systems should provide enough spatial resolution to allow obtaining satisfactory results in fNIRS-based BCI accuracy and efficiency. The still limited spatial resolution could be overcome by employing more sensitive data analysis techniques (e.g., multi-variate data analysis) to maximize the likelihood of decoding different mental states from coarse distributed brain activation patterns. The employment of multi-variate data analysis techniques might also help to deal with the (compared with non-clinical participants) lower signal-to-noise ratios in patients, that one might expect, so that it will become possible to differentiate even weaker brain signals.

Finally, fNIRS-based communication and control tools should be designed in a patient-tailored manner (e.g., individually selecting mental imagery tasks) in order to optimize the separability of fNIRS brain activation patterns for each participant and therewith increase the number of BCI commands that can be generated and implemented.

2.3.5 Potential of fNIRS for brain-computer interfacing

Taking into account the already reached state-of-the-art and the given opportunities for its further development, we consider fNIRS-based brain-computer interfacing as a promising technology with a clear potential to become beneficial not only as a possible alternative communication and environmental control means for severely motor-impaired patients but also for the diagnostic process in non-responsive patients (assessing the state of consciousness). It is quite likely that not all fMRI paradigms established for the detection of consciousness can be readily transformed into an EEG counterpart. Then, fNIRS may provide a solution such that these fMRI paradigms can also be transferred to fNIRS and applied easily at the patients’ beside.

With the enhanced use of fNIRS-based BCIs for clinical purposes, the spectrum of already available BCI methods could be further enriched which represents an important advantage as every functional brain imaging method has its own strengths. The challenge now is to consider and exploit these advantages in each individual case.

2.4 EEG-BCI

Rather than qualitatively different or even opposite diagnostic entities, the spectrum of DoC can be conceived of as a multidimensional continuum of conditions, in which the classical depictions of PVS and LiS are regarded as abstractions like a dimensionless point in geometry and a black body in physics (Kübler & Kotchoubey, 2007). From this point of view, the assessment procedure is not just directed to the separation of LiS from PVS and MCS, but to hierarchic evaluation of cognitive impairments and – even more importantly – remaining cognitive facilities which can become a basis for the later cognitive rehabilitation, wherein BCI can play an important part. Like with fMRI, the EEG can be used to build up such a hierarchical procedure.

2.4.1 Basic functions

These are functions which are directly related neither to consciousness nor to the ability to use BCI, but rather, indicate the very possibility to assess further, more important functions.

EEG background activity.

There is probably a qualitative difference between DoC patients with a moderate (4-7 Hz) and serious (1-3 Hz) slowing of the EEG background activity (Kotchoubey et al., 2005). The latter pattern has been observed in a big portion[1] of PVS patients and in many, but not in all, patients in acute coma. Patients with MCS and LiS usually display moderate slowing, as do many other patients with severe brain injuries but without DoC (Kotchoubey et al., 2005; Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Barroso y Martin, & Dominguez-Morales, in press; Schnakers, Majerus, & Laureys, 2005).

Sensory evoked potentials (EP) demonstrate the intactness or lesion of sensory ascending pathways. Auditory EP and more specifically brain stem potentials are of particular importance. This is because many DoC patients have either vision disorders or are unable to control their gaze, which makes use of visual stimuli very difficult, particularly at the initial stage of the examination. On the other hand, somatosensory and olfactory modalities can hardly be used for presenting complex cognitive stimuli, e.g., words. Therefore a large portion of the assessment of consciousness should rely upon auditory stimulation.

Automatic stimulus processing.

Even if the EP are normal or close-to-normal (and, therefore, sensory pathways lead signals from sensory organs to the cortex) it is possible that the primary cortical areas either do not receive this information or are unable to process it. In the auditory modality the primary “vertex complex” P1-N1-P2 (sometimes only one or

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[1] This term cannot be done more precisely for the following reason. Many chronic PVS patients remain at home or in homes for retired, whereas studies mostly include patients in hospitals. For example, Kotchoubey et al (2005) found very serious disorders of EEG background rhythms (severe slowing or flat EEG) in only about 20% of PVS patients. Given that patients are often admitted in hospitals if there is a diagnostic doubt, it can be suggested that the portion of extremely severe patients in the study was lower than in the population, and, therefore, that the datum 20% is an underestimation. The same bias holds true for the frequencies of other neurophysiological effects found in the examined PVS samples.

two components of the complex, e.g., N1-P2 can be recorded) indicates that the sensory cortex performs the initial stages of processing. The complex is best recorded at vertex, though it is generated in the bilateral temporal lobe. The complex should be recorded to all auditory stimuli, providing that the patient can hear them (Picton & Hillyard, 1988).

An additional sign of automatic processing in the primary auditory cortex is the so called mismatch negativity (MMN: Näätänen, 2000; Näätänen & Alho, 1995) which is recorded to the deviations from the expected acoustical pattern. The simplest deviation is the presentation of rare (10%) deviants on the background of frequent (90%) "standard stimuli". Although the MMN reflects more complex processing than N1 and P2, it is largely independent on conscious activity (Näätänen & Winkler, 1999). In healthy subjects the MMN is best recorded when they are not involved in listening, e.g., when they are watching a TV or reading an interesting book. In line with this idea of the automaticity, Kotchoubey et al. (2003) compared the MMN in DoC patients at the beginning of an EEG examination (when the patients were supposed to be in a rather good condition) and after 30 min of the examination (when they appeared to be tired). Neither in the percentage of patients demonstrating any kind of MMN, nor in the MMN amplitude and latency in those who did demonstrate there was any difference between the two conditions indicating that the MMN can probably be tested independently of a patient's actual state.

Although Kane, Butler, & Simpson (2000) used, in coma patients, an MMN paradigm with as few as 30 deviant stimuli, a larger number (around 100 deviants, which implies a total of 1000 stimuli) can be useful in order to improve the signal/noise ratio. When the tones are presented with short interstimulus intervals (in our previous studies, 400 ms onset-to-onset), a danger exists that the MMN, whose latency can vary from 100 to 200-250 ms, overlaps with the exogeneous N1 component. This confusion can be prevented by using duration deviants rather than pitch deviants, i.e., the standards are tones of 70 ms duration (5 ms rise/fall time), whereas deviants have a duration of 30 ms (Fischer et al., 1999; Fischer, Morlet, & Giard, 2000)). Further, tones of sufficient complexity should be used. (Tervaniemi, Ilvonen et al., 2000; Tervaniemi, Schröger, Saher, & Näätänen, 2000) demonstrated, in a group of healthy subjects, a larger amplitude and shorter latency of the MMN to simple harmonic tones (consisting of three harmonic frequencies, like 500+1000+1500 Hz) than to tones containing only one frequency component, and Kotchoubey et al. (2003) replicated this finding in patients with severe brain lesions. Since the MMN is mainly generated in the temporal cortex (Näätänen & Winkler, 1999), the standard earlobe or mastoid reference should not be used for its recording. A nose or neck reference can be recommended.

2.4.2 Controlled stimulus processing

The most prominent (and the easiest to record) component of event-related potentials (ERP) manifesting deep levels of controlled stimulus is the P3. This is a large (up to 15-20 µV) parietal wave peaking after 300-350 ms. The P3 strongly depends on attention and the ability of the subject to perceive the corresponding stimulus as a "target", i.e., as an information-rich signal of some particular importance (Donchin, 1981). From the neurophysiological point of view, the P3 is generated by a complex network including frontal, temporal and parietal cortical areas, which is in strong contrast with the N1-P2 complex and the MMN whose generators are largely restricted to the primary sensory cortex.

The simplest way to obtain a P3 is the so called oddball procedure (Duncan-Johnson & Donchin, 1977). Because in this procedure, like in stimulation intended to elicit an MMN, frequent standard and rare deviant tones are presented, one may try to combine them into one paradigm to record both MMN and P3 to rare stimuli. However, such a combined procedure would last for at least 12 min, because obtaining the MMN requires many stimuli, while obtaining the P3 requires longer interstimulus intervals. Therefore, we (Neumann & Kotchoubey, 2004) recommend to perform two separate procedures. In an auditory oddball with intervals 900 ms and the frequency of rare deviants 15%, a total of 200 stimuli (i.e., 30 deviants) is enough to obtain a statistically significant P3 in most patients (only 9 deviants result in a statistically significant P3 in almost every healthy adult (Bostanov & Kotchoubey, 2006) and see also progress in single trial P300 detection, e.g., Li et al, 2009). Like the MMN procedure, the auditory oddball is much more efficient when complex chords containing at least three frequency components are presented rather than pure sine tones (Kotchoubey et al., 2001). Unlike MMN, however, the deviants can differ from standards in pitch rather than duration (see also Halder et al., 2010). Furthermore, salience of the stimuli can be incremented by increasing tone duration to 100 ms.

There is considerable evidence that the parietal P3 (also called P3b, see below) is one of the most reliable correlates of conscious awareness (for review, see Kotchoubey, 2005b). All manipulation with consciousness, from stimulus masking to anesthesia, first of all lead to a dramatic decrease and disappearance of the P3, even when all other ERP components remain unchanged. Nevertheless, several reports of P3 in sleep contradict this pattern. The controversy is still waiting for its solution. One of the most difficult methodological issues concerns the distinction between this wave and an earlier and more anterior P3a. The P3a, in contrast to P3b, does not necessarily require concentration and controlled processing. The discrimination is usually easy in healthy subjects in which the P3a has a frontal maximum. In patients with severe brain damage the topography of the waves can, however, be different (Kotchoubey, 2005a). In sleep, K-complexes might under some conditions simulate a P3a or even P3b.

2.4.3 Responses to highly significant stimuli

The own name.

A person's own name has a particular significance. Fischler, Jin, Boaz, Perry, & Childers (1987) were the first to demonstrate that the P3 a subject's own name is significantly larger that to another word presented with the same frequency. Perrin, Garcia-Larrea, Mauguiere, & Bastuji (1999) found that this response can also be demonstrated during REM sleep, and later on the similar differential P3 were recorded in MCS (Kotchoubey, Lang, Herb, Maurer, & Birbaumer, 2004; Perrin et al., 2006), PVS (Perrin et al., 2006; Staffen, Kronbichler, Aichhorn, Mair, & Ladurner, 2006), LiS (Perrin et al., 2006), and acute coma (Fischer, Dailler, & Morlet, 2008). Without an explicit instruction (which belongs to active procedures, see below), the response to the own name is probably highly automatic.

Emotional oddball.

In this procedure (Bostanov & Kotchoubey, 2004; Kotchoubey, Kaiser, Bostanov, Lutzenberger, & Birbaumer, 2009) five emotional exclamations are presented in a randomized order, each with a probability of 0.2. Four of them are expressions of joy and happiness, and one is the expression of woe and sadness. All exclamations are semantically empty, i.e., they are not words. Moreover, one of the joyful exclamations has the same vocalization structure as the sad exclamation ("ooh!"). A critical requirement is that the sad exclamation must be neither the most nor the least loud, and that its fundamental frequency is neither the highest nor the lowest among the 5 stimuli. Another requirement is that the stimuli should be tested in a representative group of healthy subjects to demonstrate that they are unequivocally associated with the corresponding emotions. The findings to date indicate that the rare affective stimulus elicits, not a P3, but a negative wave with a peak latency around 300 ms. The wave can also be obtained in some PVS patients and in virtually all LiS patients (Kotchoubey et al., 2009).

2.4.4 Semantic processing

Two tasks are usually employed to check EEG indicators of semantic processing: word pairs and sentences. In the former task (Bentin, McCarthy, & Wood, 1985), patients are presented with word pairs in which the second word is either semantically related (e.g., cat-dog) or unrelated (e.g., cat-moon). In the latter (Kutas & Hillyard, 1980); auditory version of Connolly & Phillips, 1994) short sentences are presented, in which, similarly, the last word is either semantically congruent with the whole sentence or not (e.g., *He wears pants, shoes and socks* versus *He drinks coffee with milk and socks*). In both instances semantic incongruence elicits a negative ERP wave N400 (according to its typical latency of 400 ms), but in the sentence task the negativity is usually of shorter duration and accompanied by a later parietal positive complex LPC (sometimes also called P600, although its peak latency is usually longer than 600 ms). Whereas in healthy subjects the effect is much larger in sentences than word pairs, this does not hold true for severely brain damaged patients who frequently show an N400 only in word pairs but not in sentences.

There is much debate about the role of conscious and other controlled processes in these ERP effects. At least, there is clear evidence that the N400 in the word pair task can be completely automatic and need not attentional control from the subject (Kiefer, 2002; Kiefer & Spitzer, 2000). This is much less clear as concerns the N400 in sentences (Schön & Besson, 2002). Regarding the LPC most experts' opinions converge on the hypothesis that this late component reflects conscious operations with word meaning (Juottanen, Revonsuo, & Lang, 1996; Kiefer & Brendel, 2006; Misra & Holcomb, 2003). This is in line with the idea that the LPC is a variety of the P3 which was discussed above as a possible correlate of conscious stimulus perception. Although it is too early to definitely conclude that a patient who shows an LPC is conscious, this is a strong indicator that other, active tasks should be used to check for consciousness.

2.4.5 Active tasks

As described in the fMRI section, passive tasks can only tell us about automatic and sub-conscious information processing. The ultimate proof of conscious awareness can only be obtained with paradigms that require conscious processing of stimuli and compliance to task instructions. The simplest approach is to use the paradigms described in the above section and turn them from passive to active by asking the participant not only to listen but to pay attention to specific stimuli, such as the deviant in the oddball paradigm. Particularly, the parietal P300 can be elicited without an active instruction, but increases substantially when subjects are instructed, e.g., to count a rare stimulus in a sequence containing frequent and rare stimuli. For example, in a semantic oddball task subjects are presented words of 5 semantic classes (e.g., animals, plants, tools, occupations, body parts), each with equal probability of 0.2. A discriminative response is elicited only with an instruction to count words of a particular class (e.g., animals, body parts (Kotchoubey and Lang, 2001)). A similar paradigm with subjects' own and other names was used by Schnakers and colleagues to investigate conscious processing in a patient with total locked-in syndrome after basal artery thrombosis (Schnakers et al., 2009). The P300 elicited by the patients' own name was significantly larger in amplitude as compared to when the patient was asked to count other names. Whereas in a standard oddball an *increase* of the P300 amplitude indicates the patients' ability to follow instructions, in the semantic oddball it is *the very presence* of any discriminative response which proves this ability.

The transition from active paradigms to voluntary intentional communication can be instantiated by a BCI. The so-called P300-BCI is well established with severely paralysed and locked-in patients (e.g., Nijboer et al., 2008). Several efforts were undertaken to present the visual P300 matrix auditorily (Furdea et al., 2009; Klobassa et al., 2009). The problems here are manifold. First, visual information can be presented in parallel whereas auditory presentation has to be sequentially. Secondly, the many items of the matrix have to be coded by fewer auditory stimuli and thus, the user has to know by heart the coding system. Finally, auditory stimulation cannot be as rapidly as visual stimulation and thus, more time is need for each selection. This in turn means that the subjects have to focus their attention for a longer period of time which may present a problem for patients in the non-responsive state. To conclude, the P300 matrix for selection of items which is commonly used in BCI paradigms is far too complex for application in non-responsive patients. Thus, much simpler approaches have to be established. To accommodate the need for simple yes/no communication Halder and colleagues developed an oddball paradigm for binary choices. Within a stream of standard stimuli two clearly distinguishable deviants were presented. These target tones differed from the standards either in frequency, amplitude or duration. The BCI successfully detected to which of the tones the subject paid attention, showing that this approach could be used for yes/no communication. Using modulation of sound direction, Schreuder and colleagues presented healthy subjects with an auditory P300 paradigm. Stimuli were presented with a circle of speakers in the centre of which the subject was seated. The speaker attended by the subjects could be detected with around 90% accuracy. These paradigms have to be tested for their viability in locked-in and non-responsive patients. A so-called 4-choice speller was introduced by Sellers and Donchin (2006). Healthy subjects and patients with ALS were confronted with 4 visual or auditory (or both) stimuli, namely, “yes, no, pass, end”. This paradigm is also aiming at yes/no communication. By introducing two irrelevant stimuli, the probability for the important target word ‘yes’ or ‘no’ is reduced to 25% which is low enough to elicit a P300. This paradigm as well as the 5x5 auditory matrix (Furdea et al., 2009) was tested with Locked-in (ALS) patients (Kübler et al., 2009). All patients had a P300 to simulation, but classification accuracy was lower than in the visual paradigm.

Most recently, the proof-of-principle was also demonstrated for a tactile P300-based BCI (Brouwer and van Erp, 2010). Twelve tactile stimulators were placed around the subjects’ waist. Subjects wore normal cloths and no placement on the skin was necessary. Participants had attend to either 2, 4 or 6 targets and a P300 to the attended target stimuli could be clearly detected. For detailed description of the state-of-the art of P300 BCIs see D6.2

Another class of event-related potential that can be used in active paradigms and then in BCIs are steady-state-evoked potentials (SSEP). These are elicited by visual, auditory or somatosensory repetitive stimulation of specific frequency. The brain’s evoked response to this stimulation is of the same frequency and its harmonics as the stimulation frequency and can be detected over the primary visual, auditory or somatosensory areas. Typically, subjects are confronted with a set of stimulators of specific frequencies and are required to pay attention to one of the stimulators. By determining the most prominent steady-state-evoked potential of the EEG it can be deduced to which stimulus the subject focuses his or her attention (Müller-Putz et al., 2005; Bakardjian et al., 2009). To accommodate for the possibly impaired eye movement in locked-in or non-responsive patients Allison and colleagues (2010) presented subjects with overlapping stimuli and required to focus attention to one of them. Although classification accuracy was not yet satisfactorily, the target stimulus could be successfully detected in 7 of 14 subjects. Somatosensory steady state evoked potentials were also used as input for BCI (Müller et al., 2001) and could be used for an active paradigm. Generally, the SSEP paradigms are “active” when patients are required to focus their attention on one of the presented stimuli and an SSEP can be detected accordingly. They, become a BCI when patients can use the paradigms for intentional selection of responses, such as yes and no which can be allocated to a specific set of stimuli. For detailed description of the state-of-the art of SSEP BCIs see D6.2

The brain’s particular activation when imagining motor actions has also been used for active tasks and as input signal for BCI. This is a simple active task permitting a reliable classification between, e.g. the patterns of differential cortical activation in the right versus left motor hand area (Neuper et al., 2005). Kotchoubey and colleagues (2003) reported a completely locked-in patient whose slow EEG activity significantly differed according to the instruction to “try” left and right hand movements. This finding strongly suggested that the patient really intended to make this movements although no movements was possible.

In many studies with healthy volunteers it has been demonstrated that modulation of sensorimotor rhythms (SMR) by means of motor imagery produced clearly distinguishable EEG patterns (Cincotti et al., 2003; Wolpaw et al., 1991). EEG patterns during motor imagery are similar to those seen during motor execution (Lotze et al., 1999). Specifically, the activation of SMA seems to be crucial for good performance in a motor imagery based BCI (Halder et al., in preparation for publication). Thus, it was not at all clear whether patients with motor cortical degeneration such as seen in Amyotrophic Lateral Sclerosis or with lesions in motor areas would be able to achieve control of SMR. Kübler and colleagues (2005) were able to demonstrate that locked-in patients with ALS could learn to modulate SMR and perform above 70% correct with a motor imagery based BCI. Patients after stroke with damage in motor areas were also shown to be able to learn SMR-control (Buch et al., 2008). Thus, SMR-based BCIs are likely to be feasible for non-responsive patients.

As with the evoked-potential based BCIs, SMR-BCIs were also adapted to the non-visual modality. Nijboer and colleagues (2008) demonstrated that SMR-modulation can be learned with auditory feedback albeit slower. Likewise Cincotti and colleagues proved that SMR can also be modulated when provided with tactile feedback (Cincotti et al., 2007). For a detailed review of SMR-based BCI see D6.2.

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