CHAPTER 9

# Brain–computer interfaces for patients with disorders of consciousness

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## Abstract

The disorders of consciousness refer to clinical conditions that follow a severe head injury. Patients diagnosed as in a vegetative state lack awareness, while patients diagnosed as in a minimally conscious state retain fluctuating awareness. However, it is a challenge to accurately diagnose these disorders with clinical assessments of behavior. To improve diagnostic accuracy, neuroimaging-based approaches have been developed to detect the presence or absence of awareness in patients who lack overt responsiveness. For the small subset of patients who retain awareness, brain–computer interfaces could serve as tools for communication and environmental control. Here we review the existing literature concerning the sensory and cognitive abilities of patients with disorders of consciousness with respect to existing brain–computer interface designs. We highlight the challenges of device development for this special population and address some of the most promising approaches for future investigations.

## Keywords

Disorders of consciousness, Vegetative state, Minimally conscious state, Awareness detection, Covert cognition

## 1 THE DISORDERS OF CONSCIOUSNESS

Severe head injury can result in clinical conditions characterized by absent or reduced awareness—known as the vegetative state (VS, or unresponsive wakefulness syndrome, UWS) and the minimally conscious state (MCS), respectively (Bernat, 2006; Laureys et al., 2010). These conditions, along with coma, are known as the disorders of consciousness (DoC; refer to Table 1 for a summary). The comatose state is an acute condition (4 weeks or less) in which a patient lacks both

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**Table 1** Overview of the Disorders of Consciousness

| Diagnosis | Characteristics | Defining Behavior | Behavioral Command Following and Communication |
|---|---|---|---|
| Coma (Bernat, 2006) | The absence of wakefulness and responsiveness to stimulation for a period of no more than about 4 weeks | Closed eyes with no responsiveness to stimulation | None |
| Vegetative state/unresponsive wakefulness syndrome [VS/UWS] (Bernat, 2006; Laureys et al., 2010; Multi-Society Task Force on PVS, 1994a,b; Royal College of Physicians Working Group, 2003) | Wakefulness with reflexive behavior | Spontaneous eye-opening behavior with no reproducible responsiveness to stimulation, excluding the following reflexive behavior:<br>startle responses (auditory or visual);<br>abnormal posturing;<br>withdrawal (motor);<br>reflexive oral movements; and/or<br>localization to sound | None |
| Minimally conscious state *minus* [MCS −] (Bruno et al., 2011, 2012; Giacino et al., 2002) | Wakefulness with nonreflexive behavior | Reproducible, nonreflexive behavior including at least one of:<br>visual fixation or pursuit;<br>object localization, recognition, or manipulation;<br>orientation to noxious stimulation; or<br>automatic motor responses | None |
| Minimally conscious state *plus* [MCS +] (Bruno et al., 2011, 2012; Giacino et al., 2002) | Wakefulness with nonreflexive behavior and command following | Behavioral command following generally accompanied by behavior indicative of an MCS − | At least one of:<br>reproducible or consistent movement to command;<br>intelligible verbalization; or<br>nonfunctional, intentional communication |
| Emergence from a minimally conscious state (EMCS) (Giacino et al., 2002) | Wakefulness with sophisticated nonreflexive behavior including functional object use and/or accurate functional communication | Accurate functional communication and/or functional object use generally accompanied by behavior indicative of an MCS + | At least one of:<br>accurate functional communication; or<br>functional object use |

Notes. *All behavioral criteria (third and fourth columns) are taken from the revised version of the Coma Recovery Scale (Kalmar and Giacino, 2005).*

awareness and wakefulness (Bernat, 2006). Following emergence from coma, patients diagnosed as in either a VS/UWS or an MCS demonstrate eye opening that reflects the preservation of the ascending reticular activating system (Fernández-Espejo and Owen, 2013; Giacino et al., 2014; Royal College of Physicians Working Group, 2003). Critically, however, a patient must produce evidence of purposeful behavior in a formal clinical assessment to be considered aware. Patients in a VS/UWS do not generate purposeful behavior and are thus considered to lack awareness (Multi-Society Task Force on PVS, 1994a,b). Conversely, patients in an MCS generate variable, but reproducible, behavior and are considered to possess awareness (Giacino et al., 2002).

A critical diagnostic marker in DoC is whether or not a patient can follow commands. While purposeful behavior is considered sufficient to denote awareness of one's external environment, command following indicates beyond reasonable doubt that the patient is conscious (Fernández-Espejo and Owen, 2013; Gosseries et al., 2014; Owen, 2013). For patients diagnosed as in an MCS, the ability to follow commands can be indicated by a diagnostic qualifier of "+" (ie, MCS+, Bruno et al., 2011, 2012). Similarly, patients in an MCS who do not demonstrate evidence of command following can be categorized as in an MCS− (Bruno et al., 2011, 2012). Emergence from an MCS (EMCS) occurs when a patient demonstrates functional object use and/or accurate communication (Giacino et al., 2002).

Given that patients diagnosed as in a VS/UWS do not produce any evidence of overt, purposeful behavior, such a patient could not follow commands in a behavioral assessment. However, factors such as fluctuating arousal, fatigue, lack of interest, and concurrent cognitive and sensory limitations from brain injury may reduce responsiveness in any patient (Giacino et al., 2014; Whyte et al., 2013). In fact, using only medical observation, misdiagnosis of a patient's conscious state is estimated at rates as high as 43% (Andrews et al., 1996; Schnakers et al., 2009b). Furthermore, there is a risk that a patient who retains awareness, but lacks the ability to respond in a behavioral assessment due to motor impairments, could be inaccurately diagnosed as in a vegetative, ie, unconscious, state. This possibility, with its implied legal, ethical, and moral challenges (Jennett, 2002; Peterson et al., 2013; Racine and Illes, 2007), has been the subject of increasing attention in scientific and clinical research for the past 20 years (Fernández-Espejo and Owen, 2013; Giacino et al., 2014; Gosseries et al., 2014).

## 2 THE CHALLENGES OF COMMUNICATING WITH A DAMAGED BRAIN

To address the diagnostic challenges of the DoC, researchers have used measures of brain function to determine if an outwardly nonresponsive patient can volitionally modulate their brain activity and provide evidence of their ability to follow commands. One well-established paradigm to assess so-called covert command following in the DoC involves asking a patient to engage in mental imagery during a functional magnetic resonance imaging (fMRI) scan (Bardin et al., 2011;

Boly et al., 2007; Fernández-Espejo and Owen, 2013; Gibson et al., 2014b; Monti et al., 2010; Owen et al., 2006; Stender et al., 2014). The patient's engagement in the mental task is quantified by the patient's ability to generate specific, reliable modulations of their brain activity identified from validation studies (Adapa et al., 2014; Boly et al., 2007; Davis et al., 2007; Fernández-Espejo et al., 2014; Naci et al., 2013; Owen and Coleman, 2007). Similar approaches using electroencephalographic (EEG) responses to imagined movement have also been used successfully in this patient population (Cruse et al., 2011a, 2012; Gibson et al., 2014b; Goldfine et al., 2011).

Given this large body of evidence that a subset of patients with DoC possess covert awareness, these patients are candidates for intervention with brain–computer interfaces (BCIs). However, an important difference between the DoC and other BCI target populations is that the DoC arise from severe and often diffuse acquired brain injury (Bernat, 2006). Most patients with DoC lack oculomotor control, which reduces the feasibility of visual information in BCI applications (Kalmar and Giacino, 2005). Significantly, the sensory and cognitive abilities of any patient with a DoC are potentially compromised by their acquired brain injuries and concurrent medical complications (Giacino et al., 2014; Whyte et al., 2013). For instance, patients in an MCS in particular are susceptible to aphasia (Majerus et al., 2009), and patients with severe brain injury, even with sophisticated abilities consistent with EMCS, can have difficultly answering yes/no questions (Nakase-Richardson et al., 2008). Patients with DoC also suffer from fatigue and fluctuating arousal (Fernández-Espejo and Owen, 2013; Giacino et al., 2014; Laureys et al., 2004). Together, these factors restrict many aspects of BCI development and anticipated BCI literacy in this population.

Despite these challenges, BCI development for patients with DoC can fulfill important clinical diagnostic functions, such as cognitive assessment and awareness detection (Boly et al., 2007; Kirschner et al., 2015; Naci and Owen, 2013; Owen et al., 2006; Rodriguez Moreno et al., 2010). In a rehabilitation context, when a purposeful external behavior is identified, efforts are focused on training the patient to employ this purposeful behavior for communication. Consequently, if a purposeful ability to covertly follow commands can be identified with BCI methods—reflecting the preservation of at least minimal consciousness—we are compelled to conduct additional investigations into feasible communication options for these patients. However, Gabriel and colleagues (2015) recently evaluated the sensitivity of fMRI- and EEG-based assessments of command following and communication using the mental imagery approaches originally reported by Owen (Boly et al., 2007; Monti et al., 2010; Owen et al., 2006) and Cruse (Cruse et al., 2011a). In the EEG assessments, positive evidence of command following and successful communication was only achieved by 6 of the 20 healthy volunteers. From the fMRI assessment, positive evidence of command following was obtained for 17 of 20 participants, but only 12 of 20 participants were able to communicate (Gabriel et al., 2015). These findings emphasize the difficulties of translating methods for the detection of command following into methods for functional communication, despite the potential diagnostic benefits.

# 3 BCIs FOR PATIENTS WITH DoC

In this chapter, we review the existing literature concerning the assessment of cognitive and sensory abilities for patients with DoC. We focus our review on neural signals that have also been used in BCI applications outside of DoC, including both healthy and patient populations. Indeed, relatively few investigations have directly evaluated BCI use in patients with DoC. Accordingly, here we highlight the available literature and discuss the feasibility of eventual BCI use in patients with DoC. We have structured our review according to the technology used to obtain the BCI control signal of interest (see Fig. 1); given the extensive study of EEG data in BCI applications to date, the majority of our review focuses on control signals acquired using this approach. In each section, we begin with a brief discussion of the neural basis of the control signal of interest, and we then discuss each subtype of paradigm according to its relevance for patients with DoC. We conclude with specific recommendations for future BCI development in patients with DoC.

## 3.1 ELECTROENCEPHALOGRAPHY

Even for healthy users, BCIs based on EEG are widely regarded as the most practical for regular use (Chatelle et al., 2012, 2015; Naci et al., 2012; Nicolas-Alonso and Gomez-Gil, 2012). EEG signals have a very high temporal resolution alongside a minimally invasive acquisition protocol. Importantly, these signals can be acquired from most individuals with minimal health risks. One of the only physical or medical attributes of a person that would render EEG measurements uninformative is a skull breach; EEG data acquired over a breached area of a skull are usually contaminated by sharp, high-frequency bursts known as breach rhythm (Lee et al., 2010). Breach rhythm occurs in some patients with DoC (eg, due to traumatic brain injury).

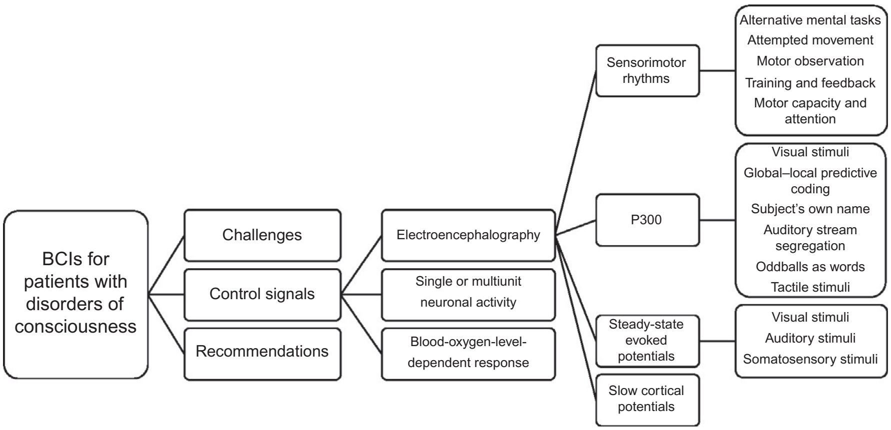


**FIG. 1**

Graphical overview of the contents of this chapter.

EEG signals are used routinely in clinical practice. Some clinical applications of EEG include the detection of epileptiform activity and monitoring during various stages of recovery from coma (Brown et al., 2010). From this clinical literature as reviewed in Bagnato et al. (2014), a reduction in EEG amplitude is associated with poor outcomes in comatose patients following cardiac arrest (Cloostermans et al., 2012; Hofmeijer et al., 2014; Synek, 1988). With respect to patients with chronic DoC (ie, those diagnosed as in a VS/UWS or MCS), several investigations have concluded that there are no general patterns of EEG responses that are specific to only one of these disorders (Bagnato et al., 2010; Boccagni et al., 2011; Kulkarni et al., 2007). Nevertheless, other researchers and clinicians have noted that patients recover more power in the alpha (8–12 Hz) and beta (13–30 Hz) bands of the EEG signal as they emerge from coma toward a VS/UWS, MCS, and recovery (Brown et al., 2010).

The EEG signal arises from summated postsynaptic potentials that occur in cortical layers known as dipole sheets (Nunez and Srinivasan, 2006). As these measures are acquired at the scalp, EEG signals are susceptible to nonneuronal electrical signals (Srinivasan, 2012). One such signal is high-frequency line noise from the alternating current of powerline electricity, although line noise is typically eliminated during acquisition (or offline) with a notch filter. Other physical sources of nonneuronal electrical signals in EEG recordings include mechanical sources, such as low-frequency signal due to the physical movement of cables or other recording devices, and transient high-frequency activity from the electrodes themselves (Srinivasan, 2012). Finally, another nonneuronal signal source that is particularly important for BCI applications with patients who lack voluntary motor control are other biological electrical signals. Biological artifacts in the EEG arise from the heart and other muscles and may also present as low-frequency drifts due to sweating. Contamination of the EEG by motion or sweating artifacts is especially problematic in studies of patients with DoC.

In BCI applications, EEG signals are frequently evaluated after being time-locked to a stimulus or response of interest and averaged over repeated presentations. This averaged, time-locked EEG signal is known as an event-related potential (ERP; Luck, 2014). ERP studies of patients with DoC were recently reviewed by Lehembre et al. (2012).

### 3.1.1 Sensorimotor rhythms

Sensorimotor rhythms (SMRs) are oscillations in magnetic or electric fields recorded over sensorimotor cortex in the mu (8–12 Hz), beta (18–30 Hz), and gamma (30–200 Hz) frequency bands (Jasper and Pendfield, 1949; Lopes da Silva, 1991; Neuper and Pfurtscheller, 2001). An event-related desynchronization (ERD) is a reduction in oscillatory activity related to a sensorimotor event (Pfurtscheller and Aranibar, 1977). An increase in oscillatory activity known as an event-related synchronization (ERS) can also occur, and this increase in activity may be a correlate of a disinhibited/deactivated cortical network (Pfurtscheller, 1992).

Low-frequency mu ERDs (8–10 Hz) occur with almost any motor behavior and are widespread over sensorimotor cortex (Pfurtscheller et al., 2000b). These oscillations are thought to reflect general motor preparation, low-level bottom-up stimulus processing, and basic attentional processing (Klimesch, 1999). In contrast, higher frequency mu ERDs (10–13 Hz) are topographically restricted and related to specific aspects of task performance (Pfurtscheller et al., 2000b). Beta rhythms have been extensively studied in cognitive neuroscience; for a review, see Kilavik et al. (2013). Beta ERDs with a rebound ERS occur following movement (Brovelli et al., 2004). Beta ERDs are similar for active/passive movements (Cassim et al., 2001), electrical nerve stimulation (Neuper and Pfurtscheller, 2001), and motor imagery (Pfurtscheller et al., 2005). These responses also coincide with decreased excitability of motor cortical neurons, as measured using transcranial magnetic stimulation (TMS; Chen et al., 1998).

#### 3.1.1.1 Neural basis of SMRs

Using depth electrodes, it has been shown that SMRs occur in both cortical and subcortical structures. For example, mu and beta activity occurs in the thalamus, subthalamic nucleus, and pedunculopontine area (Androulidakis et al., 2008; Klostermann et al., 2007; Williams et al., 2002). The relationships among these brain regions and neural rhythms when movement occurs are complicated: for instance, a mu ERD occurs in motor cortex, a mu ERS occurs in subthalamic nuclei, and a beta ERS occurs in motor cortex, the thalamus, and subthalamic nuclei (Klostermann et al., 2007). Using simultaneous EEG-fMRI, SMRs have been localized to the primary sensorimotor cortex during actual and imagined movement (Yuan et al., 2010a). ERD magnitude is also proportional to positive blood-oxygen-level-dependent (BOLD) responses (Yuan et al., 2010b, 2011), and temporal variations in SMRs are highly correlated with the BOLD signal in the contralateral sensorimotor cortex (Logothetis et al., 2001; Yuan et al., 2011). Gamma activity is also strongly correlated with the firing rate of single neurons, and this finding has been confirmed using several electrical and magnetic neuroimaging methodologies (Ball et al., 2008; Brookes et al., 2005; Lachaux et al., 2007; Logothetis et al., 2001).

#### 3.1.1.2 SMR-based BCIs

SMR-based BCIs have been extensively studied. In fact, BCIs based on responses to motor imagery were the most widely studied type of BCI between 2007 and 2011 according to a recent meta-analysis (Hwang et al., 2013). There have been many studies of SMRs for BCI applications, including cursor control (Bai et al., 2008), communication (Blankertz et al., 2006; Rohani et al., 2013), games (Marshall et al., 2013), and the restoration of motor function (Pfurtscheller et al., 2000a, 2003). Notably, better performance has been reported in the general population with the P300-based BCIs to be discussed in a subsequent section (Guger et al., 2009) than with SMR-based BCIs (Guger et al., 2003). Some investigators have recommended P300-based BCIs over SMR-based BCIs for patient applications (Nijboer et al., 2010). Nonetheless, and despite possible changes in the cortical motor system due to prolonged immobility, there is evidence that people with severe and long-term motor impairments retain SMRs and can even operate SMR-based BCIs in some cases. For example, although amyotrophic lateral sclerosis (ALS) impacts cortical motor neurons (Kiernan et al., 2011), Kübler and colleagues showed that four patients with ALS could operate a SMR-based BCI (Kübler et al., 2005). Likewise, successful SMR-based BCI use has been reported for people with muscular dystrophy (Cincotti et al., 2008), cerebral palsy (Neuper et al., 2003), spinal cord injuries (Wolpaw and McFarland, 2004), and tetraplegia (Pfurtscheller et al., 2000a). It is therefore not surprising that some patients with DoC have been found to generate reliable SMRs.

One cohort study of SMR modulations in patients with DoC was conducted by Cruse et al. (2011a). Sixteen patients and 12 healthy volunteers were instructed to imagine moving their right hand in a squeezing motion and wiggling their toes on separate trials. On other trials, participants were instructed to relax. Each experimental block consisted of fifteen 600-Hz tones every few seconds after the instruction to cue the participants to engage in motor imagery or relaxation, as instructed. Data were analyzed from 25 electrodes over motor cortex. Classification analyses employed a linear support vector machine with block-wise cross-validation. The features were log power values of the EEG data taken from 0.5 to 3.5 s after the cue, and spectral power was analyzed in four frequency bands (7–13, 13–19, 19–25, and 25–30 Hz). Accuracy was calculated with a binomial test. Above-chance classification accuracy was obtained for three patients diagnosed as in a VS/UWS (range: 61–78%, mean of 70%). These findings were taken as evidence of the abilities of these patients to follow commands (Cruse et al., 2011a).

More recently, Coyle and colleagues reported a BCI based on SMRs using visual and stereo auditory feedback with a sample of four patients diagnosed as in an MCS (Coyle et al., 2015). SMRs were obtained by asking the patients to imagine movements of the right hand or the toes with simultaneous visual and auditory cues (an arrow presented on a computer screen and a tone presented binaurally). The patients were trained in multiple sessions and provided with both visual and auditory feedback. Visual feedback consisted of visually presented games; in one version, participants had to direct a ball to a basket using hand or toe imagery to move the ball left or right, respectively. Auditory feedback consisted of a short clip of music or pink noise moved between the left or right earphones using the same imagined movements. The patients produced significant, appropriate, and consistent responses across multiple assessments. Auditory feedback seemed to enhance arousal more than visual feedback, and the music feedback resulted in better performance than pink noise. Overall, this study provides strong evidence that a true BCI is feasible for use by patients with DoC (Coyle et al., 2015).

An important consideration with respect to machine learning methods to identify subject-specific responses in the absence of overt behavior (or other means to confirm the subject-specific effects) is that these techniques are susceptible to task-irrelevant changes in the EEG. In response to the previously discussed work of Cruse et al. (2011a), Goldfine and colleagues highlighted the potential problems of blocked mental imagery tasks (Goldfine et al., 2013). Using blocks circumvents the potential for so-called automatic responses due to task instructions (Owen et al., 2007), but also introduces potential violations of certain statistical assumptions that may lead to high rates of false positives (Cruse et al., 2011b; Goldfine et al., 2013). Notably, the rate of false positives can be reduced by increasing the amount of features available from the EEG data for these machine learning approaches (Noirhomme et al., 2014). However, as has been discussed elsewhere (Cruse et al., 2014a; Peterson et al., 2015), applications intended to inform the diagnosis of the DoC especially require a case-by-case trade-off between an acceptable rate of false alarms (ie, evidence of command following when the patient lacks awareness) and misses (ie, no evidence of command following when the patient is aware).

***3.1.1.2.1 Alternative mental tasks.*** Despite the interest and reasonable success of SMR-based BCIs, there have been some concerns over the practicality of their use. As noted in two recent reviews, SMR-based BCI performance is quite variable in healthy samples (Grosse-Wentrup and Schölkopf, 2013; Yuan and He, 2014). Some investigators have employed motor imagery questionnaires to determine if these measures predict BCI performance success (Hammer et al., 2012; Vuckovic and Osuagwu, 2013). Unfortunately, these approaches are not appropriate for patients with DoC. It has also been proposed that using different mental tasks, including more complex or familiar actions, could improve performance (Chatelle et al., 2012; Curran and Stokes, 2003; Curran et al., 2004). In fact, Gibson and colleagues found that more complex bimanual movements and certain types of familiar movements led to more robust SMR modulations in a sample of healthy individuals (Gibson et al., 2014a). Similarly, one recent study of patients who had suffered strokes found an advantage for user-selected mental tasks over experimenter-selected tasks (Scherer et al., 2015). These alternative mental task approaches have also been evaluated in patients with DoC.

One of the first reports of alternative motor imagery tasks to evaluate SMR modulations in patients with DoC was that of Goldfine et al. (2011). Two patients with DoC (one diagnosed as in an MCS and the other diagnosed as EMCS) and one patient with locked-in syndrome (LIS; León-Carrión et al., 2002; Smith and Delargy, 2005) were asked to imagine swimming and to imagine moving around their homes. In this approach, alternating instructions to start and stop imagination were presented approximately every 15 s. EEG data were analyzed from 29 or 37 electrodes, and these electrodes were converted to a Laplacian montage to improve source localization (Hjorth, 1975). Power spectral density was calculated from 4 to 24 Hz. In the univariate approach to the statistical analysis of the spectral data, $z$-statistics were calculated using the two-group test (Bokil et al., 2007). In the multivariate approach, the investigators employed Fisher's linear discriminant analysis (LDA). A randomization test with a false discovery rate-corrected probability threshold was used to assess the statistical significance of these analyses (Goldfine et al., 2011).

The healthy volunteers generated statistically reliable, but variable (across participants), SMR modulations to imagined swimming and spatial navigation (Goldfine et al., 2011). The most common finding from the healthy volunteers for imagined swimming was an ERD from 6 to 9 Hz and 13 to 15 Hz in central channels. For spatial navigation, however, no two healthy volunteers generated the same type of SMR modulation. From the patient sample, the patient with LIS and one patient diagnosed as in an MCS also generated reliable SMR modulations for imagined swimming (Goldfine et al., 2011). One patient produced a reliable ERS from

11 to 20 Hz that was maximal at parietal sites, while the other patient produced a reliable ERS from 8 to 12 Hz alongside a reliable ERD from 15 to 17 Hz. The investigators noted that these two patients, as well as the third patient, produced indeterminate results on some runs (Goldfine et al., 2011).

The investigators speculated about the reason for the indeterminate results from some of the patients in their sample (Goldfine et al., 2011). Possible sources of variability include differences in task performance between runs, diminished EEG signals, and, in the case of the third patient (with no determinant results on any run), subclinical seizure activity. The presence of a statistically reliable modulation of the SMR from the two patients in this report was taken as evidence of their ability to follow commands (Goldfine et al., 2011). In a subsequent fMRI study, one patient diagnosed as in an MCS, one patient diagnosed as in an EMCS, and one patient with LIS generated responses in the supplementary motor area (SMA) and premotor cortex (like healthy volunteers) when instructed to perform motor imagery involving actions from tennis, swimming, or another subject-specific activity (Bardin et al., 2011). Taken together, these studies confirm the utility of different types of motor imagery to detect SMRs from patients with DoC.

Using a similar approach, a small sample of patients with DoC completed motor imagery tasks in separate evaluations with fMRI and EEG (Gibson et al., 2014b). In the EEG assessment, the patients were asked to imagine squeezing their right hand or to imagine performing a hand action from a sport or other action that was familiar to them based on consultation with a family member. In the fMRI task, the patients were asked to imagine playing tennis and moving around their home, as has been previously reported (Boly et al., 2007; Monti et al., 2010; Owen et al., 2006). EEG data were analyzed in a bipolar montage over sensorimotor cortex from sites C3′ (FC3-CP3) and C4′ (FC4-CP4) between 7 and 30 Hz. A spectral analysis procedure consisting of a nonparametric *t*-test with a Monte Carlo approach for estimating *p* values was used to assess the presence or absence of SMRs (Maris, 2004; Maris and Oostenveld, 2007).

One patient diagnosed as in an MCS+ (ie, with behavioral command following) and one patient diagnosed as in a VS/UWS generated robust SMR modulations for imagined movements of their right hand (Gibson et al., 2014b). Both patients produced ERDs that were statistically significant over the contralateral hemisphere in the mu (7–13 Hz) range. Only the patient diagnosed as in a VS produced evidence of reliable and appropriate responses to the two imagery tasks during the functional scans; these findings were taken as corroborative evidence for the patient's ability to follow commands. The patient diagnosed as in an MCS+ did not produce reliable and appropriate brain responses during the fMRI assessment, and this finding was interpreted as reflective of the patient's fluctuating ability to sustain attention and arousal. An overview of these findings is presented in Fig. 2 (Gibson et al., 2014b).

***3.1.1.2.2 Attempted movement.*** Another approach to SMR modulation assessment for patients with DoC is to ask the patients to attempt to complete a motor action. Cruse and colleagues evaluated this paradigm in a case report of a patient diagnosed as in a VS/UWS (Cruse et al., 2012). The patient was instructed to try to move his left or right hand with alternating periods of rest. Classification of SMR modulation was performed using a Naïve Bayes classifier with 10-fold cross-validation. The features for classification were logarithmic power values from 7 to 30 Hz. Only EEG data from sites C3′ (FC3-CP3) and C4′ (FC4-CP4) were analyzed, and statistical significance of the classification procedure was determined using a familywise permutation test (Maris, 2004).

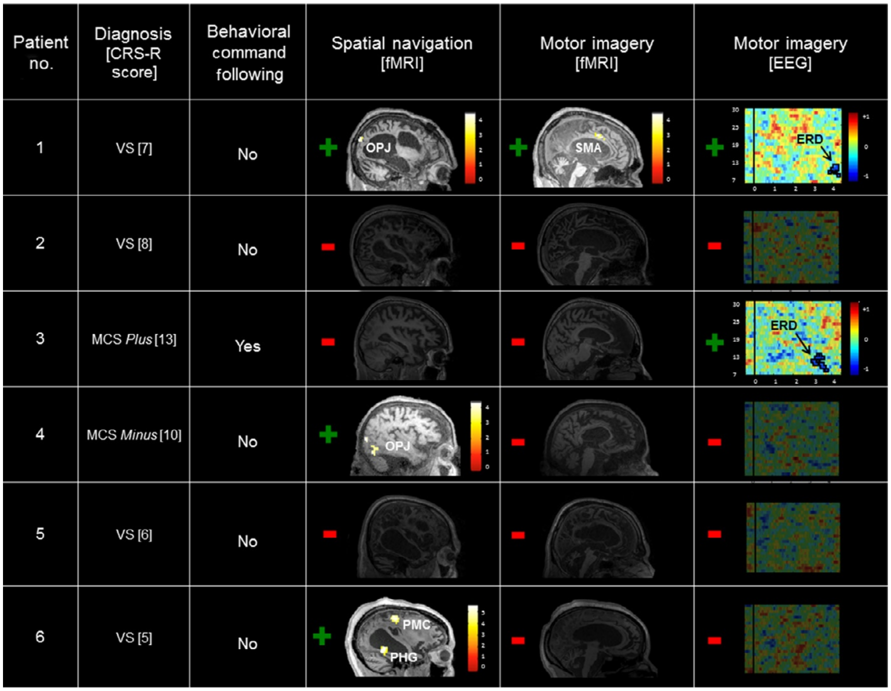


**FIG. 2**

Summary of the results of six patients with DoC on behavioral, fMRI, and EEG-based assessments of command following. Significant BOLD responses for the fMRI mental imagery tasks are indicated by region on each patient's T1 image. Significant SMR modulations from the EEG motor imagery task are enclosed with a black outline on each spectrogram. Note that both patients with statistically significant SMR modulations generated ERDs over contralateral motor cortex from 7 to 13 Hz. CRS-R, Coma Recovery Scale—Revised; VS, vegetative state; MCS, minimally conscious state; OPJ, occipito-parietal junction; SMA, supplementary motor area; PMC, premotor cortex; PHG, parahippocampal gyrus; ERD, event-related desynchronization.

*Reproduced with permission from R. Gibson from the original open-source publication (Gibson R.M., Chennu S., Owen A.M. and Cruse D., Complexity and familiarity enhance single-trial detectability of imagined movements with electroencephalography, Clin. Neurophysiol.* ***125****, 2014a, 1556–1567; Gibson R.M., Fernández-Espejo D., Gonzalez-Lara L.E., Kwan B.Y., Lee D.H., Owen A.M. and Cruse D., Multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness, Front. Hum. Neurosci.* ***8****, 2014b, 1–9).*

As in the previously discussed investigations, the SMR modulations from the healthy volunteers were variable (Cruse et al., 2012). For example, two volunteers produced statistically significant ERDs in the 7–13 Hz band, while three other volunteers produced only statistically significant ERSs in different frequency bands (Fig. 3; Cruse et al., 2012). Importantly, however, significant SMR modulations only occurred for attempted movement and never for the rest periods. The patient generated a statistically significant ERS over the ipsilateral hemisphere for attempted movements of his left hand in the frequency range of 25–30 Hz. This ERS began about 0.5 s after the instruction and dissipated about 1 s later (Fig. 4; Cruse et al., 2012). This finding was taken as evidence for the patient′s abilities to follow commands (Cruse et al., 2012).

Attempted movement paradigms for patients with DoC have also been evaluated using fMRI (Bekinschtein et al., 2011). In this study, all patients first underwent a separate assessment with fMRI to determine whether or not they had the ability to process basic speech stimuli. Five patients diagnosed as in a VS/UWS with preserved auditory processing were identified using this approach. These five patients then underwent an fMRI scan while receiving verbal instructions to move their left or right hand with alternating periods of rest. Interestingly, two of the five patients diagnosed as in a VS/UWS generated premotor activity in response to the commands to attempt movement, like healthy volunteers. These findings were again taken as evidence of the abilities of the two patients with positive results to follow commands (Bekinschtein et al., 2011).

Another report of alternative mental tasks intended to elicit reliable SMR modulations from patients with DoC, including attempted movement, is that of Horki et al. (2014). A sample of six patients diagnosed as in an MCS were asked to perform mental imagery for certain sports, spatial navigation, and attempted movement of their feet. Four patients participated in an offline paradigm, while four patients (two from the offline paradigm) participated in an online paradigm with feedback. Classification analyses were performed using an LDA classifier. Features were computed from logarithmic band power in five frequency bands from 4 to 30 Hz, and data were converted to a Laplacian montage. Nested block-wise cross-validation was applied in both the online and offline analyses; the offline procedure involved a $10 \times 10$ inner fold and a leave-one-out-block outer fold, and the online procedure involved a $10 \times 10$ inner fold, leave-one-out-block outer fold, and microaveraging of confusion matrices. Online analyses were only applied to the motor imagery conditions (imagined movement of the feet and sport imagery). For feedback, correctly classified trials were followed by "Sport/feet correctly recognized," while other trials (incorrect or indeterminate due to artifacts) were followed by "Pause" (Horki et al., 2014).

All three mental tasks rendered classification accuracy above 50% in all four patients (Horki et al., 2014). Significant results were obtained for sport imagery in 10/18 sessions; attempted feet movement in 7/14 sessions; and spatial navigation in 4/12 sessions. In the online procedure, three of the four patients also produced classification accuracy above chance in either the attempted movement or sport imagery tasks. Of note, all classification analyses actually conducted online in the

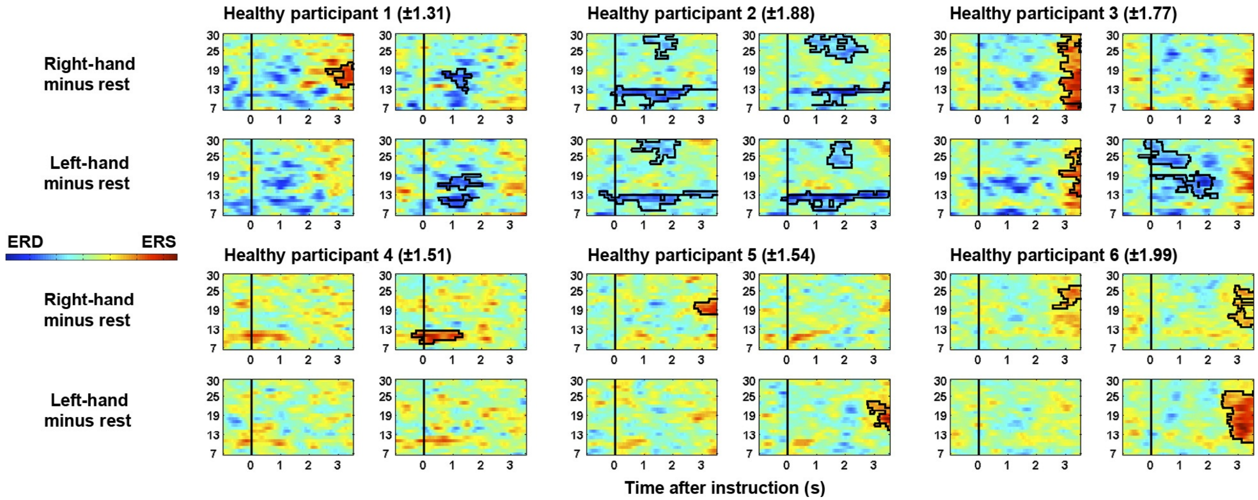


**FIG. 3**

Single-subject modulations of SMRs in a sample of six healthy young adults. The participants engaged in imagined movements of their left and right hands, with significant modulations enclosed in black on each spectrogram. The range of power values (log ratio vs rest) that are plotted is indicated in parentheses. Plots on the left and right for each participant reflect left- and right-hemisphere EEG channels (C3' and C4' respectively). Time is measured relative to the offset of the verbal instructions. Frequency (Hz) is indicated on the vertical axis.

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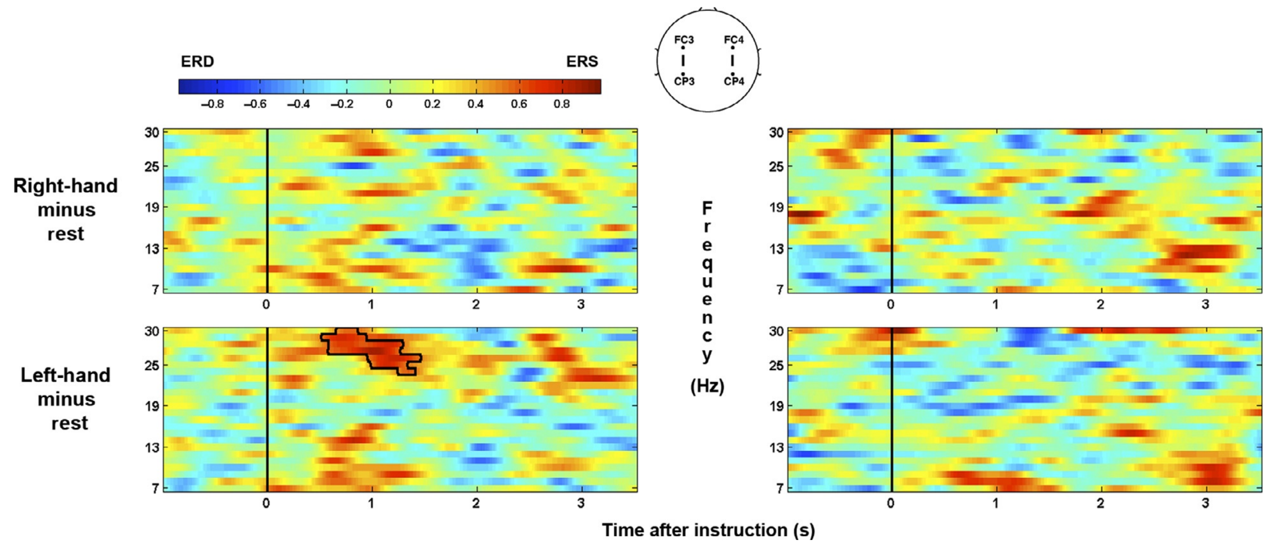


**FIG. 4**

Modulation of SMRs in one patient diagnosed as in a VS/UWS. The patient produced a reliable ERS for attempted movements of his left hand from 25 to 30 Hz from about 0.5 to 1.5 s after the cue, as indicated with a black outline on the appropriate spectrogram. Plots on the left and right reflect left- and right-hemisphere EEG channels (C3' and C4' respectively). Time is measured relative to the offset of the verbal instructions. Color scale denotes the log ratio of power versus rest.

*Reproduced with permission from D. Cruse from the original open-source publication (Cruse D., Chennu S., Fernández-Espejo D., Payne W.L., Young G.B. and Owen A.M., Detecting awareness in the vegetative state: electroencephalographic evidence for attempted movements to command, PLoS One **7**, 2012, e49933).*

online portion of the task were below chance, and the reported above-chance classification analyses of this session were calculated offline. The authors speculate that a shorter detection period after the instruction to engage in mental imagery was needed to detect the SMR changes online. Additionally, as in previous reports (Cruse et al., 2011a; Goldfine et al., 2011), the SMR modulations generated by the patients were variable in terms of both topography and frequency (Horki et al., 2014).

***3.1.1.2.3 Motor observation.*** Another approach to examine SMR modulations in patients with DoC has combined motor observation with motor imagination. In a sample of nine patients diagnosed as in a VS/UWS and seven patients diagnosed as in an MCS, Lechinger and colleagues presented participants with a short film of a person reaching for, and then drinking from, a mug (Lechinger et al., 2013). As participants watched the video, they were instructed to imagine completing the same movement. Once the video ended, the participants were asked to engage in motor imagery of the same action again. Following this, an image of two resting arms was presented. EEG data were analyzed over three topographies: frontal, F3 and F4; central, C3 and C4; and parieto-occipital, PO7 and PO8. SMRs were evaluated from complex Morlet waves calculated between 1 and 30 Hz, and statistical significance was determined using an ANOVA with factors of diagnostic group, scalp location, and time (baseline, motor observation, and motor imagery; Lechinger et al. 2013).

None of the patients diagnosed as in a VS/UWS showed a reliable response to motor observation, while all patients diagnosed as in an MCS showed reliable ERDs for this condition (Lechinger et al., 2013). The SMR modulations generated by the patients were different from healthy volunteers in that the patients produced reliable patterns as an ERD from 8 to 10 Hz alongside an ERS from 12 to 15 Hz, while the volunteers produced an ERD from 8 to 15 Hz only. Nevertheless, the significant SMR modulations from the patients were taken as evidence of the ability of those patients to follow commands (Lechinger et al., 2013).

***3.1.1.2.4 The importance of training and feedback.*** Another body of work that explores performance variations in SMR-based BCIs involves the role and type of user training and feedback. One study reported that a 2-min pretraining was required to achieve a state of mind for optimal SMR-based BCI use in a healthy sample (Blankertz et al., 2010). Another investigation employed three types of feedback during SMR-based BCI training, including an animated visual bar and anatomically congruent feedback of animated hand movements (Ono et al., 2013). All types of feedback improved performance relative to users who received no feedback (Ono et al., 2013).

Coyle and colleagues have explicitly investigated the role of feedback for SMR-based BCI use in two case reports about a patient diagnosed as in an MCS (Coyle et al., 2012, 2013) and a recent cohort study of patients diagnosed as in an MCS (Coyle et al., 2015). The BCI paradigm involved imagined squeezes of the right hand and wiggling of the toes with the same stimulus presentation parameters as used in the cohort study by Cruse et al. (2011a). In Coyle's version, instructions were also given visually, with text for imagery instructions and arrows to reinforce the auditory cues to begin imagery (Coyle et al., 2012, 2013, 2015). For classification, frequency bands were selected automatically from 1 to 30 Hz using neural time-series prediction preprocessing (Coyle, 2009; Coyle et al., 2005) with neural networks and common spatial patterns with LDA (Coyle et al., 2005, 2011). A 20-fold inner–outer cross-validation was performed for parameter optimization. The final time point of the peak mean classification accuracy was used for the real-time feedback.

In the first case report, feedback consisted of visual animations (Coyle et al., 2012). The patient tried to direct a ball into a basket (first run) and to move a spaceship to dodge asteroids (second run) using toe or hand imagery to move the ball/spaceship left and right, respectively. The significance of the classification analyses was determined with a parametric *t*-test and a Wilcoxon signed-rank test. The patient generated robust SMR modulation during this task. For example, in channel C4, the patient produced an ERS during hand imagery and an ERD during toe imagery, while an upper band ERD was evident in channel C3 during hand imagery. Notably, the patient also produced significant classification accuracy during the task, with accuracy surpassing chance 3-s after the feedback (Coyle et al., 2012).

In a follow-up study, Coyle and colleagues extended their feedback and paradigm to the auditory modality (Coyle et al., 2013). In addition to the visual feedback procedure reported in Coyle et al. (2012), a secondary auditory feedback procedure was evaluated using broadband (pink) noise and music. In this case, the sounds were varied from the left to the right earphones as the patient engaged in motor imagery to move the sound left or right, as directed by spoken commands of "LEFT" and "RIGHT." The same protocol for sound movement applied as in the visual task, ie, toe imagery to move left and hand imagery to move right. Classification accuracy was similar for both types of feedback, but the difference between peak and baseline accuracy increased for auditory feedback and decreased for visual feedback. The investigators speculated that this difference may have occurred because the patient was unable to fixate on the visual information. They also noted that the patient seemed to become more alert as he received the auditory feedback (Coyle et al., 2013).

In a subsequent cohort study by Coyle and colleagues, the findings of the two case reports were confirmed and extended to three additional patients (Coyle et al., 2015). Importantly, this body of work provides evidence that feedback protocols are feasible for use by patients with DoC and that feedback can lead to performance gains for these patients (Coyle et al., 2012, 2013, 2015). Moreover, this work also confirms that musical feedback is also feasible for use by, and perhaps even leads to increased arousal from, patients with DoC (Coyle et al., 2012, 2015). Auditory feedback in particular is critical for patients with DoC due to their visual impairments. Importantly, recent investigations involving healthy volunteers have provided evidence that auditory feedback renders similar performance benefits as visual feedback (McCreadie et al., 2014; Nijboer et al., 2008). Altogether, these findings support the use of auditory information as feedback for improved BCI performance and a potentially more engaging user experience for patients with DoC.

***3.1.1.2.5 The roles of motor capacity and attention in SMR-based BCI use.*** An important application of SMR-based BCIs is movement rehabilitation for patients with impaired motor function. One investigation applied TMS to the motor cortex prior to and following SMR-based BCI training over a 4-week period in a sample of healthy people (Pichiorri et al., 2011). SMR training enhanced cortical motor excitability and resulted in functional connectivity changes in the higher-beta frequency range (Pichiorri et al., 2011). In another investigation of healthy volunteers, motor imagery-induced ERDs were associated with enhanced M1 excitability (Takemi et al., 2013). These findings imply that motor imagery, like overt movement, can lead to changes in corticospinal excitability (Takemi et al., 2013). For patients with DoC, poor integrity of white matter tracts between motor cortex and the thalamus prevents patients who can imagine movements from being able to execute these actions (Fernández-Espejo et al., 2015; Osborne et al., 2015). Furthermore, it is unlikely that most patients with DoC have sufficient cognitive and attentional resources to participate in extended training sessions. Nevertheless, motor imagery training interventions are potentially useful for patients with DoC, although there are no reports of such attempts to date.

Another factor in SMR-based BCI use relevant to patients with DoC is performance fluctuations due to variations in attention (Grosse-Wentrup and Schölkopf, 2013). Trial-to-trial variations in SMR modulation correlate with gamma amplitude in healthy volunteers (Grosse-Wentrup and Schölkopf, 2013). This finding implies a causal role of gamma in SMR variability (Grosse-Wentrup et al., 2011). In another study of healthy volunteers, baseline gamma predicted SMR-based BCI performance success (Grosse-Wentrup and Schölkopf, 2012), and the same relationship between SMR-based BCI use and gamma held in a case study of one patient with ALS (Grosse-Wentrup, 2011). Given the prevalence of low-frequency EEG activity in patients with DoC, however, it seems unlikely that a relationship between SMR modulation stability and gamma power will be useful, although this is an empirical issue that requires additional investigation.

#### 3.1.1.3 The feasibility of SMR-based BCIs for long-term use

There are a few issues that need consideration to evaluate the feasibility of long-term use of SMR-based BCIs by patients with DoC. In one report, BCI performance and SMR patterns stayed relatively stable over 10 weeks in a sample of healthy volunteers (Friedrich et al., 2013). The volunteers also reported greater comfort in performance over time (Friedrich et al., 2013). Even with design and alternative classification approaches, however, the variable success of SMR-based BCIs in healthy people has led some researchers to recommend against motor imagery approaches for BCIs in general (Henriques et al., 2014; Nijboer et al., 2010). For functional binary communication, the lower limit of classification accuracy is argued to be 70% (Kübler et al., 2001). In a recent investigation, 38% of healthy users could not achieve performance at or above 70% with an SMR-based BCI (Hammer et al., 2012). In fact, about 20% of healthy users cannot regulate their SMRs well enough to accurately control the intended BCI application (Blankertz et al., 2010). While some reports are optimistic (Kübler et al. 2005), two recent studies of patients with ALS have reported significantly reduced SMR modulation (Kasahara et al., 2012) and abnormal motor imagery abilities (Fiori et al., 2013) in these patients. On this basis, these researchers have cautioned that SMR-based BCI use may not be appropriate for patients with ALS (Fiori et al., 2013; Kasahara et al., 2012). Despite these concerns, SMR-based BCIs are particularly promising when feedback is provided to the user, as evident from some studies of SMR-based BCI use in patients with DoC (Coyle et al., 2011, 2012, 2015). SMR-based BCIs accordingly warrant additional investigation for patients with DoC given that these devices may provide reward, stimulation, and skill development for these patients.

### 3.1.2 P300 event-related potentials

The P300 is a positive-going ERP that peaks about 300 ms after a rare stimulus (Comerchero and Polich, 1999; Picton, 1992; Polich, 2007). The so-called novelty P300 is elicited by an infrequent, oddball stimulus within a series of events from two classes. P300 amplitude decreases as the frequency of the rare event increases (Comerchero and Polich, 1999; Squires et al., 1977) and positively correlates with the time interval (up to about 8 s) between stimuli (Polich, 1990; Polich and Bondurant, 1997). Importantly, the P300 (or P3a) reflects bottom-up, preconscious processing (Comerchero and Polich, 1999; Squires et al., 1977). There is some evidence that the P300 can even be elicited during sleep (Cote, 2002) and sedation (Koelsch et al., 2006). Finally, the P300 tends to be lower amplitude in BCI applications than standard scientific investigations due to the rapid rate of stimulus presentation (Martens et al., 2009; Woldorff, 1993). This tendency is exacerbated in patients with DoC, who often produce ERPs with reduced amplitude due to cortical atrophy (Goldfine et al., 2011).

In some variations of the typical oddball paradigm with a response or attentional contingency, both P3a and P3b ERPs can be elicited (see Fig. 5). In this context, attended, task-relevant target stimuli elicit the P3b potential (Comerchero and Polich, 1999; Squires et al., 1977). The P3b differs from the P3a in that it is usually largest over parietal sites and tends to occur at a longer interval from the eliciting stimulus than the P3a (Comerchero and Polich, 1999; Polich, 2007). Importantly, the P3b reflects top-down, conscious information processing (Comerchero and Polich, 1999; Squires et al., 1977), although one very recent investigation challenges this view (Silverstein et al., 2015). With the novel and controversial work of Silverstein and colleagues aside (Silverstein et al., 2015), P3b paradigms are often employed for awareness detection applications.

#### 3.1.2.1 Neural basis of the P300

From combined EEG-fMRI investigations of the typical P300 auditory oddball task, this ERP is associated with increased activity in the SMA, anterior cingulate cortex (ACC), temporoparietal junction (TPJ), insula, and inferior frontal gyrus (Bledowski et al., 2004; Li et al., 2009; Mulert et al., 2004). From a few seminal lesion studies reviewed in Soltani and Knight (2000), it was observed that lesions in the TPJ abolished the auditory P300, whereas lesions in the lateral parietal cortex did not impact

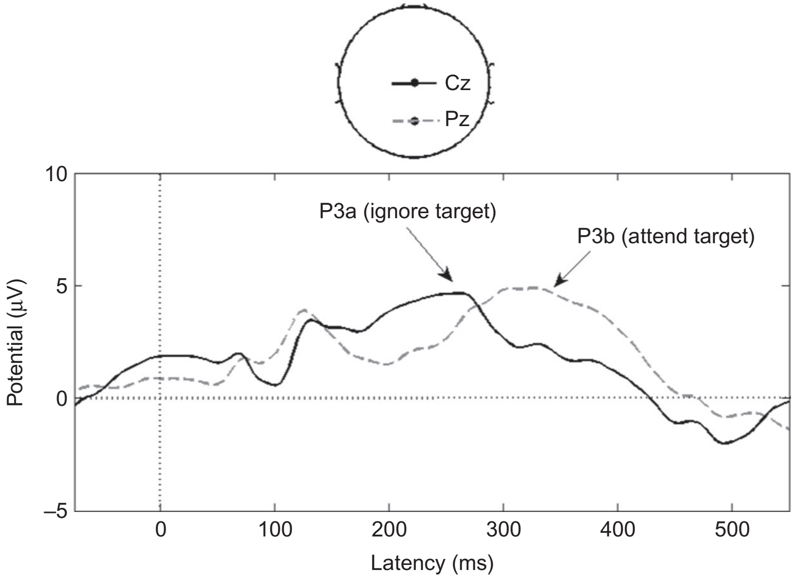


**FIG. 5**

Sample P3a and P3b grand-averaged event-related potentials as measured at scalp locations Cz and Pz, respectively. These responses were calculated from unpublished data acquired from 16 healthy volunteers by Gibson and Cruse. The locations of Cz and Pz on the scalp are depicted in the topographic map at the top of the figure. Time is measured relative to the onset of the target stimulus. Targets were presented as 10% of all stimuli, and participants were instructed to either attend to or ignore these targets in separate blocks. Unattended targets elicited P3a responses, while attended targets elicited P3b responses, as indicated.

P300 amplitude (Knight et al., 1989). Similarly, lesions in the prefrontal and lateral parietal cortex did not impair auditory, visual, or somatosensory P300s, whereas lesions of the TPJ abolished both auditory and somatosensory P300s and reduced the visual P300 (Knight and Scabini, 1998). Overall, this work suggests the P300 has a distributed set of generators in the brain and reflects complex information processing.

#### 3.1.2.2 Visual P300-based BCIs

The first report of the P300 for a communication BCI application was the [visual] P300 speller described by Farwell and Donchin (1988). This speller used a $6 \times 6$ grid of incrementally flashed letters, and while spelling rates were relatively low by modern BCI standards (2.3 characters per minute), this early approach was effective. Since its original report, several subsequent studies have reported modifications and variations of this original design. For example, an innovative variation of the original speller paradigm used a checkerboard pattern (rather than a grid) to eliminate issues of simultaneously flashing targets, and this led to fewer errors due to users selecting an unintended item within the same row or column as the intended target letter (Townsend et al., 2010). Despite the promise and relative success of the visual

P300-based BCIs, the utility of these approaches for patients who lack voluntary motor control, and especially oculomotor control, is limited. For example, a few studies have found that variable gaze direction tends to reduce P300 amplitude (Brunner et al., 2010b; Treder and Blankertz, 2010). Most patients with DoC are unable to fixate their eyes and lack voluntary motor control; on this basis, one would expect very diminished (and difficult to detect) P300 responses to visual stimuli from these patients.

#### 3.1.2.3 Auditory P300-based BCIs for patients with DoC

Given the limitations of visual P300 speller BCIs for patients who lack oculomotor control, investigators have attempted to develop auditory versions of these BCIs. By combining auditory and visual stimuli, researchers have presented modified P300 spellers with a $5 \times 5$ visual matrix that maps onto auditory stimuli (Furdea et al., 2009). Another research group presented a P300 BCI with a $6 \times 6$ visual matrix that mapped onto environmental sounds (Klobassa et al., 2009). One entirely auditory approach provided users with a five-choice set of response options by giving each stimulus a unique pitch and spatial location (Schreuder et al., 2010). Importantly, there have been a few assessments of auditory P300-based BCIs for patients with LIS (Kaufmann et al., 2013; Kübler et al., 2009) and several tests of these approaches in patients with DoC, as will be discussed in detail next.

***3.1.2.3.1 Global–local predictive coding.*** One approach to assess P300s from patients with DoC employs hierarchical predictive coding (Friston, 2008). The first study of the ERP global–local predictive coding framework including patients with DoC was conducted by Bekinschtein et al. (2009). Bekinschtein's paradigm employed auditory stimuli to evaluate brain responses to violations of temporal regularity. In this approach, local violations arise following the unexpected occurrence of a deviant sound in a train of standard sounds, while global violations follow the detection of a deviation in the higher-order pattern of the stimuli. For patients with DoC, this approach can dissociate between automatic, stimulus-driven information processing and higher-order, top-down expectations about incoming sensory information (Bekinschtein et al., 2009).

From healthy volunteers, it was determined that the ERP response to local deviations was an early response in auditory cortex known as the mismatch negativity (MMN; Bekinschtein et al., 2009). Conversely, global deviations led to a P3b. In a second sample of healthy volunteers, the same local response occurred even when participants were instructed to mind-wander and ignore the sounds. Furthermore, the local response also occurred when participants were engaged in a concurrent rapid serial visual response task. In contrast, the global response was abolished in both the inattentive and visual distraction conditions, confirming that the detection of global violations only occurs when subjects are attentive and aware of the violations (Bekinschtein et al., 2009). Most importantly for our purposes, Bekinschtein and colleagues evaluated responses to the global–local framework in a sample of four patients with DoC (Bekinschtein et al., 2009; see Table 2). Interestingly, the global responses were detected only in three of the four patients diagnosed as in an MCS. These three patients showed subsequent clinical improvement such that all

**Table 2** Overview of the Patient Outcomes from the Global–Local Predictive Coding Investigations Discussed in This Subsection

| Investigation | Local Response | Global Response |
|---|---|---|
| Bekinschtein et al. (2009) | 3/4 VS/UWS | 0/4 VS/UWS |
| | 4/4 MCS | 3/4 MCS |
| Faugeras et al. (2011) | 22/22 VS/UWS | 2/22 VS/UWS |
| Faugeras et al. (2012) | 6/24 VS/UWS | 2/24 VS/UWS |
| | 9/28 MCS | 4/28 MCS |
| | 8/13 Conscious patients | 7/13 Conscious patients |

three patients had progressed to a fully conscious state several weeks after their assessment with the global–local paradigm. Overall, the absence of the global effect in the patients diagnosed as in a VS/UWS suggests that this effect is a measure of subjective conscious content and awareness (Bekinschtein et al., 2009).

Since the original report of this global–local paradigm (Bekinschtein et al., 2009), there has been a high correspondence between global prediction errors and consciousness (Faugeras et al., 2011, 2012; King et al., 2013). Faugeras and colleagues used the same analysis of the ERP effects as in the original publication (Bekinschtein et al., 2009) alongside permutation testing (Faugeras et al., 2011). Local effects were detected in all of the patients, but global effects were only detected in two patients. Both patients with global effects had progressed to a diagnosis of MCS within 4 days of their assessments with the global–local paradigm (Faugeras et al., 2011).

In Faugeras et al. (2012), a large sample of patients with DoC were evaluated with the global–local paradigm. As reported in previous work, patients diagnosed as in a VS/UWS with global effects progressed to an MCS within a few days of their assessment with the global–local paradigm (Faugeras et al., 2012). Additionally, Faugeras and colleagues reported on an early effect of sound processing by examining the averaged ERPs from electrode Cz across an entire trial (Faugeras et al., 2012). A significant negative deflection corresponding to a contingent negative variation (CNV) was detected in all healthy volunteers, most of the patients in the conscious group, many of the patients in the MCS group, and some of the patients in the VS/UWS group (see Table 2). Importantly, all patients with a significant CNV had global effects, and all patients without significant CNV effects did not have global effects. There was no apparent correspondence between the presence or absence of the CNV and the local effect. This finding suggests that the CNV reflected the participant's expectations of the stimulus regularity (Faugeras et al., 2012). Use of the CNV in BCI applications will be discussed in more detail in the subsection concerning BCIs based on slow cortical potentials (SCPs).

***3.1.2.3.2 Subject's own name.*** There have been several studies concerning P300 responses from patients with DoC that utilize the patient's responses to their own first name (vs other sounds, or other/unfamiliar names). These studies are often referred to as subject's own name, or SON, approaches. Prior to their utilization in assessments of patients with DoC, it was documented that healthy volunteers produce enhanced P300 responses to SON vs other unfamiliar names (Berlad and Pratt, 1995; Wood and Cowan, 1995). During sleep stage II and paradoxical sleep, healthy volunteers also produced enhanced, but delayed, P300s to SON stimuli vs unfamiliar names (Perrin et al., 1999).

One of the earliest reports of responses to SONs in a sample of patients with DoC and LIS was that of Perrin et al. (2006). In this approach, eight prerecorded, spoken first names were presented to patients and healthy volunteers. Names included SON and seven unfamiliar, high-frequency names. In the healthy control group, SON evoked early perceptual ERP components and P300 responses (Perrin et al., 2006). For the patient sample, all patients other than two patients diagnosed as in a VS/UWS generated the same set of ERP responses including a P300. In both the healthy and patient samples, P300 responses were larger for SON than for unfamiliar names. In terms of latency, the P300 was significantly delayed in the VS/UWS group relative to the healthy group and LIS group; likewise, the P300 was significantly delayed in the MCS group relative to the control group (Perrin et al., 2006).

In a follow-up study, researchers added an attentional manipulation to the SON task for patients with DoC (Schnakers et al., 2008b). In all blocks, eight first names were presented to the patient, including SON and seven unfamiliar, high-frequency names. In the passive listening blocks, patients were simply presented with all names without any task instructions. In one set of active blocks, patients were asked to count one of the unfamiliar target names. In another set of active blocks, patients were asked to count SON (Perrin et al., 2006; see also Risetti et al., 2013).

There were no differences in any of the early perceptual ERP components for any of the diagnostic groups (Schnakers et al., 2008b). P300 waveforms differed between the healthy and MCS groups only. In the follow-up analyses, healthy individuals produced larger P300 responses for passive SON vs unfamiliar names and for counted vs uncounted targets in the active conditions. All of these group effects were also consistent at the single-subject level. For the patient sample, 9 of 14 patients diagnosed as in an MCS made a larger P300 to counted targets in one of the two active conditions; this enhanced P300 effect was used to infer command following from those patients. The P300 was significantly delayed in patients diagnosed as in an MCS relative to the healthy volunteers. The authors suggest that this latency difference from the MCS patients reflected an information processing delay (Schnakers et al., 2008b).

Using a similar paradigm, some patients with DoC generated distinct ERPs (MMN) to SON presented among tones and other names (Qin et al., 2008). Early perceptual responses and MMN to SON were detected in the EEG data from all healthy participants. For the patient sample, SON-MMN was present in two patients diagnosed as in a comatose state, three patients diagnosed as in a VS/UWS, and two patients diagnosed as in an MCS. Interestingly, at a 3-month follow-up assessment, six of the patients with SON-MMN responses had behavioral responses consistent with an MCS, while one patient (diagnosed as comatose at the initial assessment) had behavioral abilities consistent with a VS/UWS (Qin et al., 2008).

As in a previous case report (Schnakers et al., 2009a), some patients in an acutely comatose state also produced reliable P300 responses in a combined SON and tone task (Fischer et al., 2008; Schnakers et al., 2009a). Furthermore, the presence of the P300 had a high predictive value such that most patients with a preserved P300 response awakened (Fischer et al., 2008). Similar results were obtained in the cohort study of patients with chronic DoC (Fischer et al., 2010). P300 responses to SON were detected in most patients diagnosed as in a VS/UWS and half of the patients diagnosed as in an MCS. Interestingly, these components did not significantly differ in amplitude or latency between MCS and VS/UWS. Finally, fewer patients with anoxic brain injuries than with traumatic brain injuries generated P300 responses (Fischer et al., 2010).

A recent variation on the SON P300 paradigm using the subject's own face rather than name employed steady-state visual-evoked potentials, SSVEPs (Pan et al., 2014). (Note that evoked potentials for BCI applications with the DoC are discussed in a subsequent subsection.) Patients were presented with their own and unfamiliar photographs and asked to count photos on one side of the screen (left or right) as the pairs of photographs changed in a random order. The flashing frames were intended to elicit SSVEP responses, while the flashing target (left or right) was used to elicit P300 responses. After 10 s, a feedback photo was selected based on the classification procedure. Correct feedback photos were presented with a 4-s sound clip of applause (Pan et al., 2014).

Data were collected and analyzed across three experimental runs. In the first run, the patients were asked to focus on their own photo. Five patients achieved accuracy greater than 64% in this run (two VS/UWS, two MCS, and one LIS). In the second run, patients were instructed to attend to the unfamiliar photos. Three of the five patients with above-chance accuracy in the first run also achieved accuracy greater than 64% in this run (one VS/UWS, one MCS, and one LIS). In the third run, patients were asked to attend to their own or the unfamiliar photo in a random order, and the same three patients again generated classification accuracy greater than 64%. The investigators concluded that these three patients were able to follow commands and thus possessed awareness (Pan et al., 2014).

To infer the brain areas involved in brain responses to SON, a few previous studies have measured brain responses from patients with DoC while participating in similar versions of the EEG paradigms described previously and undergoing an fMRI scan. Some patients with DoC generated responses in the ACC (Qin et al., 2010), auditory association cortex (Di et al., 2007), and medial prefrontal cortex (Staffen et al., 2006) when attending to their own vs unfamiliar names and/or sounds. Additionally, two patients diagnosed as in a VS/UWS who produced activation in association temporal cortex to SON, ie, areas involved in the higher-order processing of sounds, showed clinical improvement at a 3-month follow-up visit (Di et al., 2007). Altogether, these studies support the utility of SON approaches for detection of command following in patients with DoC.

***3.1.2.3.3 Auditory stream segregation.*** A number of other P300-based BCI-like frameworks have also been evaluated for use by patients with DoC. In a study by Halder and colleagues, an oddball task based on auditory stimuli was used for binary communication with healthy volunteers (Halder et al., 2010). The binary response options were given with two low-frequency deviant tones such that participants directed their attention to the deviant tone type that corresponded with their desired response (Halder et al., 2010). In another study of only healthy volunteers, Kanoh and colleagues developed a P300-based BCI using responses to auditory stream segregation (Kanoh et al., 2008). Concurrent streams of two different tones (ie, high or low pitched) were presented to the right ear with occasional deviants in each stream. Participants were able to direct their attention to one of the two streams such that they produced P300s to the deviant tones in the attended stream (Kanoh et al., 2008).

Pokorny and colleagues sought to develop a P300-based BCI with auditory stimuli that allowed for binary decisions (as in Halder et al., 2010) and did not rely on binaural hearing (as in Kanoh et al., 2008; Pokorny et al., 2013). This paradigm was assessed in a sample of healthy volunteers and 12 patients diagnosed as in an MCS. A stream of high and low tones with occasional deviants in each stream was presented to both ears. EEG data were acquired from 15 sites in the healthy volunteers, but only from 9 sites in the patients due to time constraints and the challenges of positioning electrodes on participants who were lying in bed. Healthy participants were always presented with the two concurrent streams of tones, while the patients were always initially assessed using only one of the two streams in order to assess a P300 response in the traditional manner (Pokorny et al., 2013).

Pokorny and colleagues used a machine learning approach to identify P300 responses (Pokorny et al., 2013). P300 classification was conducted for deviant vs standard tones only in the single stream condition (baseline); deviant tones were compared to standard tones in each stream separately; and deviant tones from the attended stream were compared to deviant tones from the unattended stream. Classification accuracy for the healthy volunteers ranged from 59% to 64.5% in all comparisons. For patients, however, classification accuracy was always below chance. On this basis, none of the 12 patients diagnosed as in an MCS generated reliable P300 responses, and thus did not demonstrate command following, with this approach (Pokorny et al., 2013). We speculate that the cognitive demands of stream segregation are too high for patients with DoC.

***3.1.2.3.4 Oddballs as words.*** As is necessary for most BCI paradigms, some patients with DoC retain normal (or nearly normal) language comprehension (Coleman et al., 2007, 2009; Davis et al., 2007; Fernández-Espejo et al., 2008). Partly capitalizing on this finding, one approach to P300-based BCIs for patients with DoC employed word stimuli (Chennu et al., 2013). The stimuli consisted of emotionally neutral, monosyllabic, spoken words. In a block, about two-thirds of the words were assigned as irrelevant distractors, while "YES" and "NO" were presented repeatedly among these distractors. "YES" was always presented to the left ear, while "NO" was always presented to the right ear to allow participants to allocate spatial attention differently between the two targets. This differential allocation of spatial attention was intended to facilitate a participant's ability to selectively attend to one word or the other. Across blocks, either "YES" or "NO" was assigned as the target word such that the other word became an implicit target due to its high frequency and distinct spatial orientation (Chennu et al., 2013).

Chennu and colleagues evaluated each patient's data for the presence or absence of P3a responses to implicit targets and P3b responses to explicit targets (Chennu et al., 2013). ERPs were identified using a nonparametric *t*-test (Maris and Oostenveld, 2007) comparing global field power, GFP (Lehmann and Skrandies, 1980; Skrandies, 1990), from both conditions with a Monte Carlo approach for estimating *p* values (Maris, 2004). The comparison of the GFP difference at each time point to the maximal GFP difference obtained in each iteration controls for familywise error and multiple comparisons. These controls are important in studies that employ high-density electrode arrays (in this case, 129 channels). The GFP data were compared between the −300 to 0 ms prestimulus window and the 100–400 ms poststimulus for the P3a and with 400–700 ms poststimulus for the P3b (Chennu et al., 2013).

Explicit target words were associated with P3b responses (Chennu et al., 2013). Specifically, implicit targets elicited only P3a responses, while explicit targets elicited only P3b responses in the group analyses of the EEG data from the healthy volunteers. These results were consistent at the single-subject level for all healthy volunteers, with the exception that P3a responses were also elicited by explicit targets for five of eight volunteers. At the group level, both explicit and implicit targets elicited P3a responses from the patients, while neither type of target elicited a P3b from the patients. At the single-subject level, 17 of the 21 patients did not show significantly different ERP effects for standard vs deviant stimuli. However, both a P3b response to explicit targets and an (abnormally) early P3a response to implicit targets were identified in one patient diagnosed as in a VS/UWS. This patient also generated evidence of covert command following in an fMRI motor imagery paradigm (Boly et al., 2007; Monti et al., 2010; Owen et al., 2006). The remaining three patients, all diagnosed as in an MCS, only generated evidence of P3a responses, but none of these patients generated quantifiably different responses to explicit and implicit targets (Chennu et al., 2013).

Another variation on the oddball word paradigm intended for patients with DoC involves a more limited set of auditory stimuli (Lulé et al., 2013). This approach was developed for healthy volunteers and patients with ALS (Furdea et al., 2009; Sellers and Donchin, 2006). Four words ("YES," "NO," "STOP," and "GO") were presented with two speakers positioned in front of the participants (Lulé et al., 2013). In a block, each word was presented 15 times in a pseudo-random order, and participants were asked to count the occurrences of either "YES" or "NO" to detect their ability to follow commands. Subsequently, participants were asked to answer yes/no questions by attending to the desired response. P300 responses were detected using a permutation test and the robust average method (Litvak et al., 2011). Classification analyses were performed using stepwise LDA (Lulé et al., 2013).

P300 responses were detected in 12 of 16 healthy volunteers (Lulé et al., 2013). Communication accuracy from the healthy volunteers was 73% online on average. P300 responses were also detected in one patient diagnosed as in an MCS and one patient with LIS, although the P300 response from the patient diagnosed as in an

MCS was only significant at one electrode (T8). For communication, one patient with LIS achieved classification accuracy of 60%, while the other patient with LIS achieved classification accuracy of only 20%. None of the patients with DoC, including four patients diagnosed as in an MCS+, achieved above-chance classification accuracy during the communication task and thus could not use the BCI (Lulé et al., 2013).

Similar paradigms involving word stimuli have been evaluated for patients with DoC using fMRI. In one approach involving similar word stimuli as in Chennu et al. (2013), each patient was asked to select and maintain an arbitrary target word in mind throughout an experimental block (Monti et al., 2009). One patient diagnosed as in an MCS generated activation in the frontoparietal network during this task, which implied that the patient had both working memory and target detection abilities (Monti et al., 2009). Similar evidence that some patients with DoC can sustain their attention was reported by Naci and colleagues in two other fMRI studies (Naci and Owen, 2013; Naci et al., 2013). As in Chennu et al. (2013), patients were asked to count "YES" or "NO" presented among other words. Two patients diagnosed as in an MCS and one patient diagnosed as in a VS/UWS produced similar frontoparietal responses as healthy individuals during this task (Naci and Owen, 2013; Naci et al., 2013). Furthermore, one patient diagnosed as in a VS/UWS and one patient diagnosed as in an MCS could answer two yes/no questions with this approach (Naci and Owen, 2013). Overall, these studies confirm that a small number of patients with DoC are capable of sustaining attention to word stimuli and can even follow commands, despite their inability to respond with their overt behavior.

#### 3.1.2.4 Tactile P300-based BCIs for patients with DoC

Another promising alternative to auditory P300-based BCIs are a family of BCIs that use tactile stimulation. These approaches have value in that they do not engage the auditory or visual systems, which leave these sensory systems available for other activities. Frontal lobe lesions have been associated with diminished oddball P300s, but preserved P3bs, to tactile stimulation (Yamaguchi and Knight, 1991). This implies that tactile stimulation may tax the attentional mechanisms that generate the P300 more so than other types of stimulation. In one early report, tactile stimulation was applied at the waist with two, four, or six tactors, and all three versions of this paradigm led to significant classification accuracy in a sample of healthy volunteers (Brouwer and van Erp, 2010).

Another study compared a tactile P300 speller BCI, in which healthy users counted vibrations on their fingers to select letters of the alphabet, to a conventional visual P300-based BCI speller (van der Waal et al., 2012). In another recent report, classification accuracy for P300 responses to tactile stimulation was substantially higher in a sample of healthy volunteers when stimulation was applied to different limbs rather than to adjacent fingers (Ortner et al., 2013). Finally, in one case study of a patient with LIS, the patient reported low practical use in daily life for the tactile BCI, and online classification accuracy was lower for this paradigm than for the auditory or visual alternatives (Kaufmann et al., 2013). However, offline accuracy was higher with tactile vs visual or auditory stimulation in this case report (Kaufmann et al., 2013).

In one recent report, some patients with LIS were able to communicate using a tactile P300-based BCI (Lugo et al., 2014). As a baseline test for the P300, tactile stimulation was applied at two places on the body; 90% of stimuli were applied at one site as the standard stimuli, while 10% of stimuli were applied at the other site to elicit the P300 response. For communication, stimulation was applied at three locations on the body such that two sites received infrequent stimulation (5% per site) to allow the patient with a binary response option. EEG data were analyzed from Fz, FC1, FC2, C3, Cz, C4, CP1, and CP2 using an LDA classifier. The first five trials served as the training data, and every subsequent five stimuli served as the test set for online classification. Feedback was given as the class with the highest sum of weight parameters from the test set (Lugo et al., 2014).

To test for the P300, the investigators conducted an ANOVA comparing voltages across all eight electrodes using a moving window of 50 ms (Lugo et al., 2014). A P300 was considered present for a significant difference between target/nontarget stimuli at a minimum of two electrodes between 200 and 600 ms poststimulus. P300 responses were detected in five of six patients with LIS in the single deviant condition and in all six patients in the two-deviant condition. However, these results varied between the testing (postfeedback) and training (prefeedback) phases. For communication, accuracy was 55.3% on average and required three to seven stimuli (Lugo et al., 2014). The feasibility of this approach for patients with DoC has yet to be assessed.

#### 3.1.2.5 P300-based BCI optimization and feasibility of long-term use

Given the popularity and efficacy of the P300-based BCIs, there is a tremendous amount of literature about the optimization of these approaches. For example, one report explicitly compared classification accuracy across different recording montages (Krusienski et al., 2008). It was found that a montage consisting of Fz, Pz, Cz, PO7, PO8, and Oz generated the best performance accuracy (Krusienski et al., 2008). Subsequently, another research group proposed an algorithm to optimize classification accuracy for P300 BCI data (Cecotti et al., 2011). In terms of classification algorithms, stepwise LDA and Fisher's linear discriminant classifiers consistently produce the best performance for this type of BCI (Krusienski et al., 2006). It has also been acknowledged that these algorithms perform optimally when the parameter settings are customized to the individual user (Sellers and Donchin, 2006). These attributes have been incorporated into some studies of patients with DoC, as discussed previously (Lugo et al. 2014; Lulé et al. 2013; Pokorny et al. 2013).

A number of sophisticated applications have been developed for P300-based BCIs. Examples include creative applications like painting (Münßinger et al., 2010) and Internet browser control (Bensch et al., 2007; Mugler et al., 2008). Given the limited cognitive abilities of most patients with DoC, these more sophisticated BCIs have not been tested in this population to date. Nonetheless, these outlets could potentially benefit a suitable patient. Additionally, Kirschner and colleagues recently proposed a battery of auditory P300-based assessments for patients with DoC that probes increasingly complex cognitive processing, including verbal reasoning and working memory (Kirschner et al., 2015). Unfortunately, this approach has yet to be evaluated in a sample of patients with DoC (Kirschner et al., 2015).

Given the popularity of the P300-based BCIs, it is not surprising that some investigators have developed tools to assess the practicality of these approaches for people with severe disabilities, such as patients with ALS (Mccane et al., 2014). In studies of long-term use, P300 amplitude changes for healthy volunteers vary within a session (Pan et al., 2000; Ravden and Polich, 1999) and over several months (Kinoshita et al., 1996). Conversely, other studies have found no change in P300 amplitude from healthy volunteers tested over 2 weeks (Polich, 1986; Williams et al., 2005). Patients with ALS had stable P300s when assessed repeatedly over 10 weeks (Sellers and Donchin, 2006), and in a single patient, over daily use for 3 years (Sellers et al., 2010). Longitudinal studies of P300-based BCIs in patients with DoC are encouraged.

### 3.1.3 Steady-state evoked potentials

A steady-state evoked potential (SSEP) is a repetitive series of voltage deflections phase-locked to a sensory event (Picton et al., 2003; Vialatte et al., 2010). A SSEP consists of a fundamental frequency corresponding to the frequency of the stimulus and its harmonics (Herrmann, 2001). SSEPs can be detected in single trials (Quian Quiroga et al., 2001) and enhanced with averaging (Dawson, 1954). More recent study has found improvements in the SSEP as a BCI control signal by classifying three harmonic peaks, including higher harmonics and subharmonics of the stimulation frequency, rather than only one or two peaks (Brunner et al., 2010a; Müller-Putz et al., 2005).

SSEPs derive from sensory cortex. Using high-density EEG, dipole modeling, and simultaneous fMRI, it was found that visually evoked SSEPs (SSVEPs) arise from the primary visual cortex, motion-sensitive association cortex (MT/V5), and, to a lesser extent, both mid- and ventral occipital areas (Di Russo et al., 2007). Using MEG and high-density EEG source localization protocols, the auditory SSEP (SSAEP) arises from primary auditory cortex (Makela and Hari, 1987; Pantev et al., 1996); these findings are supported by fMRI-based evidence that the medial primary auditory cortex in humans is always activated by sound (Petkov et al., 2004). Similarly, SSEPs to somatosensory stimulation (SSSEPs) derive from primary somatosensory cortex as assessed using surface and depth electrodes in humans (Allison et al., 1989a,b) and in animal models (Arezzo et al., 1981; McCarthy et al., 1991).

#### 3.1.3.1 Visual SSEP-based BCIs

For BCI applications, SSEPs were initially evaluated using visual stimulation. In one of the earliest investigations, users were able to move a cursor in one of four directions to navigate through a maze (Vidal, 1977). Later attempts employed a large grid, which gave the user 64 response options (Sutter, 1992). A recent study of a small group of healthy volunteers and one patient with ALS reported modest success (bit rate of 10.83 bits/min and single-subject accuracy of 80% in the patient) with a modified SSVEP paradigm in which the user could have their eyes closed while flashes were presented in a pair of glasses (Lim et al., 2013). Importantly, this eyes-closed approach could provide a binary communication option for a patient with a DoC without the need for visual fixation, but replication and validation studies are needed. Moreover, this type of BCI may be less promising for noncommunicative patients given that the flashing lights in the eyes could be irritating, especially if the patient did not wish to participate.

#### 3.1.3.2 Auditory SSEP-based BCIs

SSAEPs occur in humans for stimulation rates between 1 and 200 Hz (Picton et al., 2003). Even during sleep, SSAEPs remain relatively consistent for stimulation frequencies up to 70 Hz (Cohen et al., 1991). SSAEP-based BCIs are relatively rare. Two recent investigations (Baek et al., 2013; Kim et al., 2011) presented binary communication BCIs based on SSAEPs, but the information transfer rates of these approaches were lower than the visual equivalents. Another recent attempt combined SSAEPs with a standard oddball paradigm to elicit P300s, but found superior performance for P300 (vs SSAEP) classification (Hill and Schölkopf, 2012).

#### 3.1.3.3 Somatosensory SSEP-based BCIs

As with other sensory modalities, SSSEPs can be reliably detected following only a few seconds of stimulation (Noss et al., 1996). When elicited using vibrations (rather than nerve stimulation), cortical SSSEP amplitude is maximal with stimulation from approximately 20 to 26 Hz (Snyder, 1992; Tobimatsu et al., 1999). In clinical work, the absence of cortical SSSEPs to median nerve stimulation is predictive of poor recovery from coma (Cruse et al., 2014b; Zandbergen et al., 1998).

BCI applications of SSSEPs have only been recently addressed. Müller-Putz and colleagues present evidence that two of four users could selectively direct their attention to two different modulation frequencies of fingertip vibrations with success rates greater than 70% (Müller-Putz et al., 2006). Another proposed BCI framework combined SSSEPs with SSVEPs; performance in this framework was better than in single-modality designs (Maye et al., 2011; Zhang et al., 2007). Recently, one SSSEP-based BCI helped a healthy user control a wheelchair, although follow-up studies in a larger sample and a patient cohort are needed (Kim and Lee, 2014). As another alternative, users report that tactile feedback in other BCI paradigms feels more natural, and future applications of tactile feedback may be useful in BCI development (Chatterjee et al., 2007; Cincotti et al., 2007).

To date, exclusively SSEP-based BCIs have not been evaluated for use by patients with DoC.

### *3.1.4 Slow cortical potentials*

SCPs are time-locked and phase-locked ERPs elicited by sensorimotor events (Birbaumer et al., 1990). Most SCPs are negative deflections that arise in a latency range from 0.5 s or more preceding an actual or imagined movement (Birbaumer et al., 1990; Shibasaki and Hallett, 2006). There are several subtypes of SCPs, including: (1) the movement-related potential, a biphasic wave that follows an actual movement (Colebatch, 2007); (2) the readiness potential, a waveform that precedes a voluntary movement by about 0.5 s (Shibasaki and Hallett, 2006); and (3) the CNV, a deflection elicited by an imperative, ie, warning, stimulus that precedes a response-contingent stimulus (Rohrbaugh et al., 1976; Walter et al., 1964).

There is strong evidence from both cortical surface and depth electrodes that SCPs derive from the excitatory postsynaptic potentials of apical dendrites (Birbaumer et al., 1990; Mitzdorf, 1985). Moreover, troughs in SCPs correlate with high-frequency field potentials (Vanhatalo et al., 2004) and multiunit neural activity (Birbaumer et al., 1990). Most SCPs are movement related, and SCPs correlate with fluctuations in the fMRI-derived BOLD signal from sensorimotor cortex (He et al., 2008) and widespread activation in central, prefrontal, and parietal cortex (Hinterberger et al., 2003). The CNV, however, can mark both upcoming motor and cognitive actions; it is therefore not surprising that this response arises from the SMA and certain parts of the frontoparietal network (Gómez et al., 2007; Hultin et al., 1996; Nagai et al., 2004).

Early attempts to employ SCPs in BCI-like applications were similar to attempted applications of P300s and SMRs. For example, one approach involved using SCPs to control a cursor-like object in a neurofeedback framework (Elbert et al., 1980; Lutzenberger et al., 1979). Unfortunately, the rate of the system response to the user was slow such that a user could make one selection only every 10 s or so (Elbert et al., 1980; Lutzenberger et al., 1979). Subsequent attempts to employ SCPs for BCI applications focused on improving the rate of response. Two attempts included a case study of a SCP-based speller in a patient with ALS (Birbaumer et al., 1999) and a similar paradigm for healthy controls (Hinterberger et al., 2004). Unfortunately, it was noted in subsequent studies involving patients with ALS that many months of training were required for the patients to learn to regulate their SCPs sufficiently for cursor control (Neumann and Kübler, 2003; Neumann et al., 2004).

While the SCP-based BCIs require low cognitive demands, these approaches have several critical limitations for use by patients with DoC. First, the SCP signal is slow (Birbaumer et al., 1990; Chatelle et al., 2012; Shibasaki and Hallett, 2006). Second, SCP-based BCIs generally require extensive training for successful use. In studies of patients with ALS, training periods for successful BCI use range from a few weeks (Kübler et al., 2001) to several months (Neumann and Kübler, 2003; Neumann et al., 2004). Finally, SCPs occur in the same EEG frequency range as non-neuronal electrical signals from slow drift, sweating, and movement (He and Raichle, 2009). For this reason, these responses are often excluded from EEG data with filtering. As suggested in previous work, the most useful application of SCPs for future BCIs is likely the incorporation of this signal into another BCI framework to mark anticipatory responses (Boehm et al., 2014; Faugeras et al., 2012; Haagh and Brunia, 1985). Otherwise, given the slow rate of this signal, the high training demands of these BCIs, and the co-occurrence of this signal with nonneuronal electrical signals, SCP-based BCIs are impractical for use by patients with DoC.

## 3.2 SINGLE- OR MULTIUNIT NEURONAL ACTIVITY

Some investigators have developed BCIs based on signals acquired from electrodes on the surface of the brain or within brain tissue itself. The aim of BCI control signals from within the cranium is to achieve better control than is possible with the external signals (Andersen et al., 2004; Donoghue, 2008, 2012). For example, spikes recorded from a single neuron in the primary motor cortex can encode information about movement parameters such as force and velocity (Georgopoulos, 1988), while spikes from a single neuron in parietal and frontal areas can encode information such as plans for upcoming movements and limb kinematics (Achtman et al., 2007). Overall, such a control signal should allow for lower attentional and learning demands during BCI operation.

As reviewed in Yuan and He (2014), early reports of BCIs based on implanted sensors were tested with nonhuman primates (Ethier et al., 2012; Serruya et al., 2002; Taylor et al., 2002; Wessberg et al., 2000). However, implant-based BCIs have also been tested in several individuals with severe motor impairments. For example, one BCI allowed a user to execute multidimensional control of a computer cursor (Hochberg et al., 2006; Kim et al., 2008). Another promising BCI even allowed a user to control a robotic arm (Collinger et al., 2013, 2015; Hochberg et al., 2012).

Unfortunately, there are several issues that restrict the feasibility of these internal signals for regular BCI use. For example, single unit electrodes must be very small and require very high sampling rates (Buzsaki, 2004). In most applications, one must tether the electrode to the skull, which results in movement of the electrode due to cardiac or respiratory pulsations (Buzsaki, 2004). There can be difficulties with biocompatibility due to the immune response of the brain tissue to the implant (Shain et al., 2003) and biostability due to the degradation of the implant while it is exposed to the warm, salty environment of the human brain (Hsu et al., 2009). Furthermore, regular implant-based BCI use generally requires a technician for device calibration, and device failures could require repeated surgeries for repairs (Donoghue, 2012). Overall, these issues limit the clinical applications of implant-based BCIs for patients with DoC and other motor impairments (Simeral et al., 2011).

## 3.3 BOLD RESPONSE

The BOLD responses refer to changes in hemoglobin (Hb) that occur with brain activity (Ogawa et al., 1990). The two techniques to measure the BOLD response most relevant to BCI applications are fMRI and functional near-infrared spectroscopy (fNIRS). fMRI measures the BOLD response by tracking the relative amounts of oxygenated and deoxygenated Hb in the brain based on the magnetic properties of this molecule (Ogawa et al., 1990). fNIRS measures the BOLD response by passing near-infrared light through the skull and measuring the amount of light absorbed in the unique frequencies that correspond with the two types of Hb (Villringer et al., 1993). While both approaches are informative for BCI research and development, BCIs based on the BOLD response are somewhat impractical because blood flow changes are slow (Toronov et al., 2007).

fMRI approaches to BCIs are useful to provide anatomically specific feedback to users. In fact, fMRI is often used to explore and develop better BCI systems, for example, by localizing the brain signature of a particular mental task to determine the optimal placement of electrodes for EEG-based BCIs (Formaggio et al., 2010). fMRI has been used in several investigations of patients with DoC to assess a patient's ability to follow commands using mental imagery (Bardin et al., 2011; Boly et al., 2007; Fernández-Espejo and Owen, 2013; Gibson et al., 2014b; Monti et al., 2010; Owen et al., 2006; Stender et al., 2014). Unfortunately, fMRI technology is expensive to obtain, operate, and maintain, and these approaches are impractical for use in daily life (Birbaumer et al., 2008).

fNIRS has several appealing attributes for BCI applications. This technique is safe, noninvasive, portable, and not as sensitive to stray electrical signals as EEG (Naseer and Hong, 2015). In studies of healthy individuals, fNIRS-based BCIs have been employed successfully with motor imagery paradigms (Coyle et al., 2007) and more cognitively demanding tasks (Hwang et al., 2014). fNIRS-based BCIs have also been proposed for spelling (Sitaram et al., 2007) and binary communication (Naseer et al., 2014). One investigation of an fNIRS-based BCI intended to allow patients with ALS to communicate had moderate success, although results were better for patients who were not completely locked-in (Naito et al., 2007). Unfortunately, BCIs based on fNIRS have not been extensively tested in patients with DoC.

## 4 SUMMARY AND RECOMMENDATIONS

It is evident that a subset of patients with DoC retains a range of cognitive abilities that could be exploited for BCI-based communication, such as attention orienting and motor imagery. Indeed, BCIs based on P300 and SMRs are by far the most extensively tested types of EEG-based BCIs, even for patients with DoC. Importantly, BCIs based on P300 responses are feasible for this population, with a number of existing paradigms based on auditory stimuli already evaluated in patient samples (Bekinschtein et al., 2009; Chennu et al., 2013; Morlet and Fischer, 2014). Future work with tactile stimulation for P300-based BCIs is promising. Conversely, BCIs based on SMRs have rendered mixed results in both healthy users and patient samples. Although SMRs have proved useful for awareness detection applications in patients with DoC (Cruse et al., 2011a; Gibson et al., 2014a; Goldfine et al., 2011), additional investigation concerning appropriate feedback protocols for these patients will likely render more consistent BCI outcomes, as evident in several recent investigations (Coyle et al., 2011, 2012, 2015).

While BCIs based on SSEPs have had reasonable success in healthy samples, the feasibility of these approaches for patients with DoC is not yet known. A potential concern about SSEPs for patients with DoC is that the repetitive stimulation required in these designs could be irritating and uncomfortable for patients (Chatelle et al., 2012). The nature of this fast stimulation also limits the practicality of use in daily life. SSEP responses to tactile stimulation may be more feasible, particularly as feedback, because this type of stimulation frees the auditory and visual systems for other purposes. Indeed, some users report that tactile feedback feels more natural than other types of feedback in BCI settings (Chatterjee et al., 2007; Cincotti et al., 2007). Lastly, one work involving a P300-based BCI achieved reasonable success in a patient sample by incorporating an SSVEP into their framework (Pan et al., 2014). Future hybrid BCIs approaches warrant additional consideration.

BCIs based on SCPs are not extensively studied because this signal is slow (Birbaumer et al., 1990; Chatelle et al., 2012; Shibasaki and Hallett, 2006). Additionally, users require extensive training to learn to regulate their SCPs (Kübler et al., 2001; Neumann and Kübler, 2003; Neumann et al., 2004). The occurrence of this signal in the same frequency band as several types of nonneuronal electrical signals limits it practicality for use in BCI applications in general (He and Raichle, 2009). However, SCPs could be incorporated into BCIs based on another EEG control signal to mark anticipatory responses (Boehm et al., 2014; Haagh and Brunia, 1985). There is even evidence that this sort of response may occur in some patients with DoC in certain types of oddball paradigms intended to elicit the P300 (Faugeras et al., 2012).

Although BCIs based on signals aside from EEG have received less attention in the literature to date, these approaches have some utility for patients with DoC. For example, fMRI has been used successfully to assess command following in patients with DoC (Bardin et al., 2011; Boly et al., 2007; Fernández-Espejo and Owen, 2013; Gibson et al., 2014b; Monti et al., 2010; Owen et al., 2006; Stender et al., 2014). Although fMRI-based BCIs are impractical for daily life use, fNIRS provides a promising and practical alternative to fMRI. fNIRS-based BCIs are garnering more attention from BCI developers (for a recent review, see Naseer and Hong, 2015). Unfortunately, aside from one report in a sample of patients with ALS (Naito et al., 2007), these approaches have not yet been evaluated in many patient samples. We are optimistic about BCIs based on fNIRS control signals in future work involving patients with DoC.

BCIs based on implanted electrodes have achieved impressive performance in a few case reports (Collinger et al., 2013, 2015; Hochberg et al., 2006, 2012; Kim et al., 2008). Indeed, internal control signals seem to provide superior control over those acquired from outside of the cranium (Andersen et al., 2004; Donoghue, 2008). However, the risks associated with these invasive approaches necessitate a careful cost–benefit analysis, particularly for patients unable to provide consent for themselves. An implant-based BCI may be suitable for a patient who demonstrates consistent evidence of command following and communication by other means, but the potential risks of these BCIs are likely to outweigh the potential benefit of such devices for most patients with DoC.

Across all types of BCIs, long-term evaluations in patients with DoC are needed. It is not yet known if the cortical control signals from these patients will remain consistent over time. Moreover, inconsistency seems probable given that these patients are likely to undergo functional reorganization due to their acquired brain injuries. The role and type of feedback that is most feasible for this population is especially in need of study. Indeed, feedback has received little attention in BCIs tested in patients with DoC, although most existing studies confirm that auditory feedback is feasible and may even improve the user experience (ie, lead to increased arousal) in some patients compared to visual feedback (Coyle et al., 2012, 2013, 2015). Additionally, the inability to regulate eye movements is a diagnostic criterion for the DoC (Kalmar and Giacino, 2005). For this reason, approaches based on visual information are inappropriate for most patients with DoC. Perhaps more importantly, the cognitive, sensory, and arousal/attentional impairments of patients with severe brain injuries varies on a case-by-case basis with the particular brain regions compromised. While user customization is important for most BCI designs, these issues require special consideration in BCIs developed for patients with DoC.

Finally, an important pragmatic consideration relates to how often we should expect a patient with a DoC to communicate with a BCI. Indeed, patients who are able to follow commands are placed in a different diagnostic category (ie, MCS+) from those patients who can functionally communicate (ie, EMCS). Furthermore, the neural mechanisms that underlie these abilities are distinct (Fernández-Espejo et al., 2015; Osborne et al., 2015). Therefore, it should not surprise us that the same is also apparently true for signs of covert command following—ie, there will be patients who exhibit command following with BCI, but who are unable to use a BCI for functional communication. As a result, those patients with DoC who will be able to operate a BCI for functional communication are necessarily a subset of those patients with DoC who can follow commands. It is clear, therefore, that the primary benefit of BCI methods in DoC is the identification of covert cognition and awareness. Nevertheless, when an ability to follow commands has been identified, it behooves the clinical and BCI worlds to develop methods to allow those patients to try to exploit their residual abilities for communication.

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