Brain computer interfaces for communication with non-responsive patients

(72 characters)

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Abstract

A substantial number of patients who survive severe brain injury progress to a non-responsive state of "wakeful unawareness", referred to as a Vegetative State (VS). They appear to be awake, but show no signs of awareness of themselves, or of their environment in repeated clinical examinations. However, recent neuroimaging research demonstrates that some VS patients can respond to commands by wilfully modulating their brain activity according to instruction. Brain-computer interfaces (BCI) may allow such patients to circumvent the barriers imposed by their behavioural limitations and communicate with the outside world. However, while such devices would undoubtedly improve the quality of life for some patients and their families, developing BCI systems for behaviourally non-responsive patients presents substantial technical and clinical challenges. Here we review the state-of-the-art of BCI research across non-invasive neuroimaging technologies, and propose how such systems should be developed further to provide fully-fledged communication systems for behaviourally non-responsive populations.

Introduction

Patients with serious brain injury may be rendered behaviourally non-responsive for a variety of reasons (Table 1, 2). The locked-in syndrome (LIS) describes an individual who, as a result of acute injury to the brain stem, in particular to the anterior pons, has (almost) entirely lost the ability to produce motor actions. Following injury, it is often possible for clinicians to confirm the presence of preserved sensory, cognitive and emotional abilities in these patients on the basis of small, but reproducible movements.[8,9] In the acute phase of LIS, consciousness is frequently impaired,[10–11] especially if there is brain swelling beyond the areas immediately affected by the infarct, or where there are additional extrapontine (e.g., thalamic) infarcts.[12] However, this impairment rarely attains the level of complete or nearly complete loss of awareness, and usually disappears with the passage into the chronic phase. The most severe LIS patients, labelled as completely 'locked-in' (CLIS) are entirely unable to perform any voluntary movements, including minor motor responses such as eye-movements.[13] Such a state is sometimes observed also in patients in the advanced stages of amyotrophic lateral sclerosis (ALS),[14,15] and although the presence of consciousness in these patients is rarely questioned, progressive cognitive disturbances do occur.[16–18] In the latest stages of the disease, these disturbances may result in disorders of consciousness (DOC).

Unlike LIS patients, patients in the vegetative state (VS) are clinically diagnosed on the basis of their behavioural profile, particularly signs of wakefulness – i.e., periodic eye-opening and closing – in the absence of signs of awareness of themselves, or of the environment, rather than on the basis of a particular neural pathology.[19] Although the distribution of aetiologies and pathological features of the VS has been studied,[20] their variance among the demographic distribution of these patients, and others who are minimally conscious (MCS), or exhibit limited signs of awareness, is not known. Some patients may remain indefinitely in a VS. (See [21] for a discussion of a newly introduced term, “unresponsive wakefulness syndrome” (UWS), which aims to steer away from the negative connotations that the label ‘vegetative state’ may attract). Other patients, as they recover their ability to demonstrate inconsistent but reproducible signs of awareness, are said to progress to a minimally conscious state.[22] The clinical assessment of these patients is particularly difficult because of its reliance on the subjective interpretation of inconsistent behaviours, which are often limited by motor constraints.[23,24] It is well established that misdiagnosis occurs frequently in this patient group, with up to 40% of patients being diagnosed as VS, when they are, in fact, (minimally) aware.[5–7]

Although a clinical diagnosis of VS implies lack of consciousness and cognition, this is not necessarily always the case. EEG and fMRI studies have shown that appropriate brain responses to stimuli of varying complexity can be preserved in some patients. These include basic sensory functions[25,26] and higher cognitive processes, such as emotional,[27,28] and semantic processing.[29–33] Some patients, who behaviourally appear to be entirely vegetative, are even able to follow commands by modulating their brain activity, thereby indicating that they are consciously aware despite their clinical diagnosis.[2–4]

Table 1

Table 2

If functional neuroimaging can be employed to allow some VS patients to demonstrate that they have preserved awareness, it may also be possible to use the same technologies as a means for such patients to communicate with the outside world. In this review, we will consider the current state-of-the-art of so-called 'brain-computer interfaces' (BCI) that rely on non-invasive functional neuroimaging, and discuss their potential for application in non-responsive patients with disorders of consciousness, including VS and MCS patients. We focus mainly on experimental paradigms that would be accessible to VS patients, as these patients are the most challenging to reach, because the least in known about any residual cognition. Therefore, BCI paradigms for VS patients must be the most robust, and the least dependent on prior assumptions about a patient's cognitive abilities. The decision to focus on this group was based on the high proportion of such patients (40%), whose awareness is not detected through bedside examinations. Paradigms that are applicable to VS patients are also, generally, applicable more widely, to patients with evident signs of spared cognition (e.g., MCS). Undoubtedly, similarly to VS, MCS patients stand to benefit greatly from the development of BCI devices that might improve on the extremely limited and inconsistent communication achieved through their gestural and verbal output.

Brain-computer interfaces

Typically, BCI applications with (behaviourally) responsive participants involve analysis and classification of brain responses, produced either voluntarily, or in response to sensory stimulation, in order to infer a desired command that reflects the user's intention. The executed command brings about a state change of the BCI system that is communicated to the BCI user, for example through a visual display.[12,34] This cycle can be repeated iteratively until there is bi-directional feedback, or online communication between the user and the operator (Figure 1).[34] Such an advanced BCI system, involves reading and interpreting the user's intention in real-time, to produce physical outcomes/changes in the system, which can inform the user's subsequent response.

For conscious participants, the BCI user's intent is clear – for example, to regulate one's own brain activity, such as that which produces the sensation of chronic pain, via neurofeedback.[35] A major hurdle in communicating with behaviourally 'non-responsive' patients is the lack of *a priori* knowledge about their level of conscious awareness, cognitive capacities, and even their communicative intent. Moreover, the level of arousal, awareness and more generally, cognition, varies dramatically between patients who are truly in a VS to those who are (minimally) aware, but have been misdiagnosed as VS. Thus, to maximise the chances that any given patient will be able to respond, a BCI system for DOC patients must be as robust to this variation, and as straightforward to use, as possible.

Figure 1

Another significant challenge in the development of BCIs for DOC patients is the limited sensory processing that these patients are likely to have.[6] The majority of BCI techniques, which have been developed for conscious participants, rely on visual stimulation and feedback.[36–40] However, vision is one of the most affected senses in

DOC patients.[6,41] By definition, VS patients lack the ability to fixate on, or pursue objects in their visual field,[19] which results in highly impaired visual processing. This precludes the use of visually-based BCI systems in this group, and, moreover, the modification of such systems for use in other modalities (e.g., auditory) is not trivial.[42,43]

Below, we review BCI research in three non-invasive neuroimaging technologies, fMRI, EEG, and fNIRS, all of which may be applicable, to varying degrees, in non-responsive patients (Table 3). Invasive technologies, such as electrocorticography (ECoG), single microelectrodes (ME), or microelectrode arrays (MEA) involve implantation of electrodes in the cortex, and, therefore, provide superior signal-to-noise ratio and better detection of high-frequency oscillatory activity[44–47] than non-invasive technologies. A proof of principle study used invasive electrodes in a BCI application for patients with limited behavioural response (e.g., locked-in).[48] However, invasive technologies are of limited relevance to patients who are the main focus of this manuscript, for several reasons. Electrode implantation is often corollary of a surgical procedure in the course of a patient's treatment, and rarely an option with stable and/or chronic DOC patients. The DOC patients we consider here (VS and MCS) are not able to provide informed consent. For any research, legal approval is required from the patient's family or other legal representative. This is far less likely to be granted for invasive BCI applications, especially when they are not part of treatment protocols, as they may adversely influence the patient's health. For similar reasons, with the exception of rare cases, where the patient requires surgical intervention and the appropriate legal and ethical permissions are already in place, such research is prevented by rulings of ethics boards and other regulatory organizations. Finally, issues of financing and access to medical resources available only to acute patients with specific conditions further prohibit invasive BCI applications in DOC patients.

Table 3

fMRI-BCIs

To date, the most successful attempt to develop a BCI system for DOC patients has used fMRI, a technique that measures the changes in blood flow and oxygenation in the brain, known as haemodynamics.[49,50] FMRI has several strengths for BCI applications, including its non-invasive nature, global brain coverage of the cortex and deep sub-cortical structures, and excellent spatial resolution (in the millimetres' range).

Owen and colleagues[3] employed an fMRI-based mental imagery paradigm to assess command-following in a patient, who had been clinically diagnosed as VS, and had been unresponsive for five months. The patient was asked to imagine playing tennis (for 30 seconds), when she heard the word "tennis", and to relax (for 30 seconds), when she heard the word "relax." In a separate spatial imagery task, she was asked to imagine moving around the rooms of her home (for 30 seconds), when she heard the word "house", and to relax (for 30 seconds), when she heard the word "relax". The patient showed task-specific fMRI activation in the appropriate regions of the supplementary motor area (SMA) following the instruction to imagine playing tennis, and in the parahippocampal gyrus (PPA), the posterior parietal lobe (PPC), and the lateral premotor cortex (PMC), following the instruction to imagine moving from room to room in her house. Moreover, this activity was indistinguishable from that of healthy participants performing the same tasks (Figure 2).[4,51] The patient's fMRI activation was statistically robust, reproducible, task-appropriate, and sustained over long time-intervals (30 seconds), allowing Owen and colleagues[4] to conclude that she was responding to the commands, by performing the imagery tasks in the absence of any overt action.

Figure 2

Monti et al[3] extended this approach to demonstrate that fMRI could also be used to *communicate* with a non-responsive patient, who was assumed to be in a VS. One type of imagery (tennis or spatial navigation) was mapped to a "yes" response, and the other to a "no" response. A single neutral word "answer" was used to cue each response to a question. To decode the answers, each communication scan was compared to two 'localizer' scans, during which the patient was asked to simply imagine playing tennis, or imagine moving around his house (see [4]). Following six autobiographical questions (e.g., "Is your father's name Thomas?"), the answers that were decoded from the brain activity matched the factually correct answers (in five out of the six questions), which were unknown to the experimenters at the time. This study demonstrated that the presence of voluntary, reliable, and sustained brain activity in response to command could be used as a proxy for physical behaviour, such as movement or speech, in order to facilitate communication with non-responsive participants.[3,4,23]

In the study described above, 54 VS and MCS patients were tested and, of those, only five (four VS) showed significant changes in fMRI activation during the basic imagery tasks. One interpretation of this finding is that the diagnosis was accurate in the vast majority of cases, and the negative results reflect a genuine lack of awareness in those patients.[3] Several other factors, however, may also explain these findings. First, it is possible that this technique lacks sensitivity, and, thus, failed to show activation in patients who might have been engaged in the task. Indeed, it is known that in brain-damaged patients, the coupling of haemodynamics and neuronal firing, which lies at the basis of the fMRI signal, may be very different from that in healthy volunteers.[52,53] Alternatively, it is possible that in some patients, deficits in language comprehension, decision-making, working memory or executive function may have hampered their efforts to express themselves through the imagery task, yielding brain activity too weak to be interpreted. Consistent with this possibility, a recent report found an MCS patient who showed no distinguishable activation in the mental imagery task, but, nonetheless, was able to voluntarily modulate his brain activity by allocating visual attention in response to verbal commands.[54] Finally, in some patients, functional re-organisation of the brain following the injury may have produced highly atypical, and therefore un-interpretable, patterns of fMRI activation.

Communication via fMRI BCIs has been attempted in six other DOC patients, five MCS and one LIS.[55] Bardin et al. [55] used binary paradigms involving motor imagery, similar to those used by Monti and colleagues, and a multiple-choice paradigm, adapted from [37]. In a novel application of this four-choice paradigm, the experimenters presented each patient, at their bedside, with one playing card, which could be one out of four, differing in two dimensions (suit and face). Subsequently, while inside the fMRI scanner, each patient was aurally provided with the four options for the suit and face of the card, and was asked to perform a mental imagery task (swimming or tennis) to indicate the correct card, for each of the two dimensions. The authors reported a communication signal in one of the six patients. Although the patient showed significant brain activity to the task, this activity conveyed incorrect responses to the two questions asked, with respect to the face and the suit of the card. However, the patient was able to correctly show command following behaviourally, at the bedside, and by modulating her brain activity in the scanner, according to the instructions of the binary mental imagery task. The authors suggested that a delay in the timing of the haemodynamic signal to the patient's response might explain why the neural responses to two stimuli proximal in time could not be disambiguated with traditional fMRI analyses.[55] This study highlighted the issue of unknown delay range of the neural signal in this patient group, which could be driven by an unusual coupling of haemodynamics and neuronal firing, as compared to healthy individuals.[52,53] While the optimal interval for a reliable measurement of the neural response is not known, the 30s intervals reported by Owen, Monti and colleagues have so far yielded unequivocal results of successful communication in one patient, and command following in six patients, documented in published reports. A systematic study of the delay range would be necessary to determine the optimal response interval, and, furthermore, this parameter might differ across neuroimaging methodologies (fMRI, fNIRS, EEG).

A second patient reported by Bardin et al.[55] raised a different issue relevant to communicating with DOC patients through neuroimaging BCIs. This patient could show command following by using motor imagery (swimming) in two different visits, but could not use the motor imagery task to produce robust brain activity that could be used for binary ('yes' / 'no') communication. Several factors could be behind this patient's failure to communicate.[56,57] The patient's profile of cognitive deficit, in particular, her short-term memory reserve, may underlie her inability to communicate. Beyond command following, where the patient has to perform a task in response to a specific command, such as 'tennis' or 'swim', in order to communicate, the patient must be able to perform at least two additional processes. First, the patient must be able to find the answer to the question that is being asked. In addition, the patient must also be able to abstract the demand characteristic of the task (i.e., 'imagine playing tennis/swimming'), to a particular answer word ('yes' or 'no'), which applies in some situations (i.e., questions whose answer is that word), but not in others. A patient with a pronounced memory deficit may not be able to either think of the answer and/or, maintain in short term memory the abstract link between the arbitrary response function (i.e., a specific form of motor imagery) and the answer word to a question ('yes' or 'no'). This patient highlights the need for new paradigms that rely on more intuitive response modes, in order to maximize the chance that patients with very limited cognitive reserves will be reached.

At least the issue of delayed response might be resolved with more sophisticated neuroimaging analysis methods,[58] such as multi voxel pattern analysis (MVPA). MVPA is an fMRI analysis technique that is highly sensitive to the information content in the neural signal. Traditional univariate fMRI analyses average across activations in a brain region, and compare overall changes in signal strength between different types of conditions.[59] MVPA, on the other hand, does not discard the information relating to the *patterns* of activity within that brain region. As such, it is capable of dissociating overlapping neural patterns to different stimuli or mental state,[60,61] which could not be disentangled with univariate methods.[62] By dissociating several mental states/responses elicited by a single command,[63,64] MVPA also has the potential to expand communication from binary responses to multiple-choice answers. For example, while still some way in the future, with MVPA it may eventually be possible to ask a patient to express how much pain he/she feels on a sliding scale from 1-10, by imagining the appropriate number. In a follow up study, Bardin et al.[58] provided the first proof of principle that MVPA can decode a patient's answers elicited from a multiple-choice response paradigm. In the case described above,[55] conventional fMRI analysis could not distinguish which one was the patient's response between two choices, in each question relating to the two card features (suit or face). For each question, two options, temporally proximal in the four-choice stimuli presentation, produced statistically significant responses that were undistinguishable with univariate analysis. By contrast, an MVPA classifier was able to disambiguate the response patterns for each question, by classifying, the response to the correct option (selected prior to the scanning session) above chance, and the response to the incorrect one at chance, with a significant difference between the two classifications.

MVPA methods can also be applied in real-time,[65–68] and present exciting possibilities for communication without perceptible delay between the question and the interpretation of the response. With these methods, however, classification accuracy is strongly dependent on the amount of available fMRI data. This may be a problem for VS patients, where the scanning time is often limited for physical reasons, e.g., the patient experiences difficulty lying supine for long periods of time. Moreover, one has to consider that VS patients may become exhausted easily.

Other approaches have also been used to explore the potential uses of fMRI for BCI-related applications. In a study with healthy participants, Sorger and colleagues[37] were able to generate the differential BOLD responses necessary to answer a four-choice question within the length of a single, one minute trial. To express their choice, participants had the option of one of two tasks, performed at one of four moments in time, which were indicated by a highlighted letter on the screen and offset by five seconds one from the other. Thus, the BOLD responses could be differentiated with respect to at least two of three features of the BOLD signal: its source location, onset, and offset. An automated decoding procedure deciphered the answer by analysing the generated single-trial BOLD responses online. Participants' answers were decoded correctly with a mean accuracy of 94.9%, ranging from 75% to 100% times. This study made an important contribution, by demonstrating that single-trial (i.e., brief, or, 1 minute long) fMRI time-courses can be used as a robust source of information for decoding responses. Further, it showed that fMRI can be used to communicate multiple-choice answers online/in real time, and within a reasonable response time-scale (e.g., one minute). This length of time does not introduce excessive time pressures, and may prove patient-friendly. However, the applicability of this design for communication with non-responsive patients would be limited by its reliance on visual processing.

Although, as we have discussed, fMRI has great strengths for BCI applications, including its non-invasive nature, global brain coverage, and excellent spatial resolution of specific brains structures, it also comes with significant limitations, which restrict its widespread use in DOC patients. In particular, its high cost, lack of portability, and physical impositions on some patients (e.g. patients must not wear paramagnetic equipment, must refrain from any minor movement, and must be able to cope with the loud noise of the fMRI scanner), make it unlikely that fMRI will provide the ultimate communicative solution that DOC patients require in real life situations. FNIRS and EEG, however, are not susceptible to these same problems, and provide exciting opportunities to extend these fMRI developments.

fNIRS-BCIs

FNIRS exploits the penetrability of biological tissue by light in the near-infrared spectrum (700-1000 nm) to infer neural activity. The amount of near-infrared light at specific wavelengths that is absorbed by blood vessels varies depending on the concentration of oxygenated and deoxygenated haemoglobin.[69,70] Using head-mounted near-infrared emitters and sensors, fNIRS provides a non-invasive haemodynamic measure of cortical activity. The main advantage of fNIRS over fMRI is that it is portable. Further, in contrast to fMRI, fNIRS is also a relatively comfortable method. It is nearly noiseless, does not expose patients to a high magnetic field, thus avoiding the restrictions imposed by paramagnetic medical equipment, and is less sensitive to movement artefacts. Moreover, fNIRS is relatively affordable, less technically demanding, and easier to operate than fMRI. These qualities make fNIRS a viable technology for use at the patients’ bedside.

While in its infancy, some early applications have demonstrated the potential of fNIRS as a BCI method. Naito and colleagues[71] mapped two mental imagery tasks, 'calculation' and 'singing', to 'yes'/ 'no' responses, and were able to detect responses with fNIRS in 40% of 17 CLIS patients. The brain response for these patients could be decoded with 74% accuracy. As the first BCI method successfully applied in CLIS patients, this study highlighted the future potential of fNIRS in this field.

While fNIRS has certain benefits over fMRI, it also suffers from technological challenges that limit its application for BCI systems, at least in its current state. In particular, fNIRS only allows reliable measurement of haemodynamic responses in cortical tissue that is close to the head surface, up to approximately 3cm in depth. Thus, brain activation in deeper subcortical structures, accessible with fMRI, cannot be targeted. Moreover, the spatial resolution of fNIRS, in the range of a few cubic centimetres, is considerably lower than the resolution that can be obtained with fMRI. Thus, BCI paradigms that employ fNIRS must be based upon neural responses that are relatively broad. Future improvements in the development of multi-channel fNIRS systems promise to address this issue.[72] Another area that will benefit greatly from further research and development is that of analyses methods, which are still relatively rudimentary in fNIRS, as compared to those used for fMRI. For example, the limited spatial resolution may be overcome by employing more sensitive data analysis techniques such as MVPA, which maximize the likelihood of decoding different mental states from widely distributed brain activation patterns.

EEG-BCIs

EEG is another non-invasive, portable, and relatively inexpensive neuroimaging method that has been used extensively in BCI applications. The experience gained with its use in many populations, from healthy participants to severely paralysed and LIS patients, lends itself to application in non-responsive DOC patients. The EEG signal that is measured on the scalp results from neural activity originating in the cortex,[73] which can be captured with high temporal resolution, in the milliseconds' range. However, in contrast to fMRI, EEG provides limited spatial resolution (centimetres' range) that strongly decreases with the depth of the source. Similar to fNIRS, EEG is silent, less physically demanding for the patient (for example it can be applied in the seated and supine positions, or even when the patient is asleep), and easier to operate than fMRI. EEG is susceptible to artefacts from electromyographic activity from cranial muscles, and electrooculographic activity from eye movements, but sophisticated analysis methods can eliminate these artefacts. Below, we review the EEG markers that hold promise for BCI systems in non-responsive DOC patients, as well as a number of challenges, that, thus far, have limited the application of this technology in this patient group.

One prominent component of event-related potentials (ERPs; electrical potentials related to events/stimuli) that has been widely used for EEG-BCI applications in responsive patients is the P300 (or P3). The P300 is a large wave peaking over parietal regions 300-350ms after the presentation of a target, or, the stimulus that is being looked out for and/or that 'grabs' attention.[74] This ERP component is often investigated in the context of the so-called 'oddball paradigm',[75] in which rare deviant tones are presented among frequent standard tones, and stand out as 'oddballs' that generate a reliable P300. In healthy participants, the P300 can be elicited by passive paradigms (e.g., just listening), especially for stimuli of particular significance, like a participant's own name,[76] and increases substantially when participants actively attend, for example, by counting a rare stimulus in a sequence of sounds.[77] About 20-25% of patients with DOC show a P300 effect.[33] Moreover, the modulation of the P300 by manipulations of conscious perception, such as stimulus masking, attention manipulations, and anesthesia, highlight its usefulness as a marker of awareness. However, its amplitude increase in active paradigms, as compared to passive paradigms, is likely to be a more reliable indicator of awareness than the mere presence of this component, as the P300 can be elicited even when participants are not conscious of the stimuli.[78,79]

The active/wilful modulation of the P300 may be employed to establish an EEG BCI method, where the patient's response is expressed through attention to specific (e.g., auditory) stimuli, according to the operator's commands. Schnakers and colleagues presented a CLIS patient with her own and other people's names, and asked her to count specific names.[80] Although the patient's own name elicited a P300 in all conditions, the P300 elicited when the patient was specifically asked to count her own name was significantly larger in amplitude than that elicited to her own name when she was asked to count other names. This suggested that the patient was able to follow instructions, and consciously processed the meaning of the words she had heard. In another study, Schnakers and colleagues[81] tested 14 DOC (MCS and VS) patients with a similar technique, and showed that the MCS patients exhibited a P300 to their own names, in both active (counting) and passive (listening) conditions. Like controls, this P300 was larger in the active condition than in the passive condition, suggesting voluntary compliance with task instructions. By contrast, the VS patients did not show any P300 differences between the active and passive conditions, suggesting that they were unable to comply with task instructions in the active condition.

Similar to the study by Monti et al.[3] at least two alternative interpretations may explain the negative result observed in the VS patients. One interpretation is that the diagnosis for these patients was accurate; they were not aware of the task they were being asked to perform, and, therefore, did not produce any responses. An alternative explanation is that the task lacked sensitivity and, thus, failed to detect VS patients who retained some level of consciousness, but were perhaps unable to understand the instructions and/or to sustain attention for a long-enough period to perform the task. This paradigm may permit the detection of voluntary brain function in patients who show very limited signs of awareness, and thus, has potential to be used as a BCI communication paradigm. However, further work is needed to establish its suitability for detecting awareness in VS patients, whose attention and cognitive faculties are subject to drastic fluctuations over time, and may, therefore, be detected only by methods robust to noise and sensitive to weak responses.

A completely different approach for using the P300 modulation as a BCI method was originally proposed by Farewell & Donchin.[82] In this paradigm, participants were presented with a screen displaying a matrix of letters, A-Z, and asked to choose a letter they wished to write on the screen. Columns and rows of the matrix flashed in a pseudo-randomized order. By identifying which column and row flashed immediately prior to an evoked P300 component, it was possible to deduce that the letter at their intersection was the attended one and, therefore, the one the participant wished to write. Although this BCI technique proved very efficient for severely paralyzed and locked-in patients,[38,83] its reliance on visual presentation limits its applicability to VS patients.

Efforts to translate this paradigm to the auditory modality[42,43] have met with a number of problems, even in healthy controls. For instance, visual information can be presented in parallel, i.e., an entire matrix of 26 letters can be presented at one time, whereas equivalent auditory stimuli must be presented sequentially. Even if the many items of the matrix could be coded by fewer auditory stimuli, compared to the visual paradigm, remembering the coding system requires focusing of attention for a longer period, while keeping much of the information in short-term memory. Such cognitive demands would very likely hamper the performance of brain-damaged patients, especially those assumed to be in the VS.

Sellers and Donchin[84] introduced a simpler version of this paradigm. They developed the so-called '4-choice speller', in which participants were presented with only four visual or auditory stimuli, namely, "yes, no, pass, end". This paradigm has been tested with LIS (ALS) patients,[85] all of whom exhibited a P300 effect to the stimulation, but classification accuracies were lower in the auditory than in the visual version of the task. For reasons similar to those discussed above, DOC patients are likely to find this task more difficult than LIS patients. Other studies with late stage ALS patients have used the self-regulation of slow-cortical potentials (SCPs) to assess and train conditional learning[86] and cognitive function, including the ability to perform simple computations[87] in these patients. However, the translation of such paradigms, developed for patients who are known to be conscious and have preserved cognitive responsivity, to patients whose clinical diagnosis precludes the presence of conscious awareness (i.e., VS patients), faces several major challenges. In particular, they rely on training, which is not, generally, an option with VS/MCS patients These challenges point to the need for continued development of EEG auditory BCI paradigms that are amenable to the limitations of non-responsive (DOC), and especially VS patients.

Another type of active EEG paradigm has utilized attempted, or imagined, motor actions, which produce neural activity that can be measured with EEG, as it can with fMRI. Kotchoubey and colleagues[88] described a CLIS patient whose slow EEG activity significantly differed between trials when he was asked to “try” to move the left, as compared to the right, hand. In healthy participants, motor imagery also produces clearly distinguishable modulation of EEG sensorimotor rhythms (SMR),[89,90] similar to those seen during motor execution.[91] Kübler and colleagues (2005) showed that LIS patients with ALS could learn to modulate their SMR with more than 70% accuracy, but did not test VS patients with this paradigm.[92]

Goldfine and colleagues[93] were the first to translate to the EEG motor imagery tasks (‘imagine … swimming’/ ‘stop imagining…’) and spatial navigation tasks (‘imagine walking around … your home’/ ‘stop imagining…’) similar to those used with fMRI.[3,4,55] They tested five healthy controls and three DOC patients, two MCS and one LIS. The authors reported variability in the patients’ responses, which allowed only limited conclusions to be drawn about the applicability of these paradigms to patients with disorders of consciousness. In the first patient, the authors observed that the task-related signals were different from those observed in the healthy controls. In the second patient, the authors observed variability between the task-related signals produced during two different visits. The signal from the first visit was consistent across runs, but the signal from the second visit was inconsistent across runs, and was classified as 'indeterminate'. The third patient showed a similarly indeterminate pattern during both visits. The authors concluded that assessment of larger sample sizes of both healthy controls and patients groups would be needed before this task could be used as a clinically diagnostic tool. However, as the first study to translate to EEG the motor imagery paradigms that have been used successfully in fMRI, this work is an important proof of principle.

Cruse et al.[2] have shown the most promising application of EEG as a BCI technology for VS patients, to date (Figure 3). They instructed a group of 16 VS patients to perform two motor imagery tasks, imagining moving their right hand and imagining moving their toes. By submitting the EEG data associated with each task command to a cross-validated support vector machine classifier, Cruse et al.[2] were able to demonstrate that three of the 16 VS patients were able to reliably and consistently modulate their SMR, with classifier outputs of up to 78% accuracy. Such a result provides the necessary proof of concept for the use of motor imagery as a BCI method and, with the future application of real-time data analyses, may allow for bedside communication with VS patients.

Figure 3

Summary

We have reviewed the advantages and disadvantages of three non-invasive neuroimaging technologies (fMRI, fNIRS, and EEG) for use in BCI applications designed to communicate with non-responsive DOC patients. While the most advanced methods for this patient group have, so far, used fMRI, given its cost and lack of portability it is unlikely that fMRI will provide a long-term communication system for any individual patient. Indeed, the development of efficient and user-friendly BCI systems for non-responsive DOC patients will hinge on the translation of these advances to cheaper and more portable technologies, such as fNIRS and EEG. Cruse et al.[2] showed that detection of command following in patients previously thought to be in a VS is possible with EEG, thus moving one step closer towards bedside communication with entirely non-responsive DOC patients.

When a brain-injured patient with disorders of consciousness effectively uses a neuroimaging system to follow commands[4] and even communicate[3], a diagnosis of VS is rendered erroneous. The mismatch between a patient's clinical diagnosis and his/her level of residual cognition, detected with neuroimaging, raises questions about how to place this patient in the current spectrum of diagnostic categories. Some authors have suggested that such patients represent a new syndrome that has yet to be fully characterized.[57,94] Furthermore, there's a moral imperative to communicate and involve these patients in important life altering decisions[95] routinely made on their behalf by other people.

To enable fully-fledged real-time BCI communication, it will be important to begin by identifying those patients, whether VS or MCS, most capable of using such systems. As we have discussed, DOC patients vary dramatically in their level of arousal and awareness. The inclusion of passive fMRI[31,96] and EEG tasks[25,33,97] within a hierarchical procedure will allow for the characterisation of the spared cognitive abilities of each patient, which could then be used to determine the most appropriate form of BCI to employ in that individual.[98] Finally, BCI systems with rapid, online decoding of brain responses could be adapted to the individual needs of high-functioning patients, to enable true inter-individual communication.

Acknowledgement

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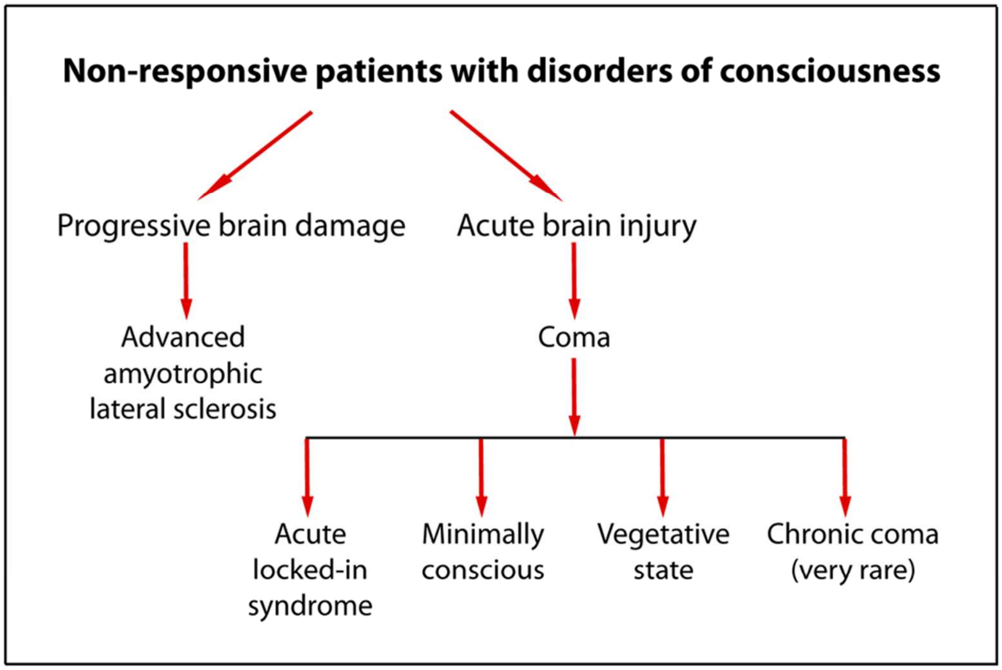


Flow chart of patient populations that exhibit non-responsive conditions.
Some patients suffering from advanced stages of progressive brain damage, such as amyotrophic lateral sclerosis, can become non-responsive. The presence of consciousness is rarely questioned in these patients. Patients suffering acute brain injury may fall into coma and develop a variety of clinical states differing in awareness and responsivity, from none to very limited. In rare cases, they may evolve to chronic coma, which is characterized by a permanent lack of wakefulness, with no spontaneous eye opening, even to intense stimulation, and lack of awareness. Other patients may progress to the vegetative state, where they display some wakefulness, including eye opening and stimulus-induced arousal, but no awareness of themselves or of their environment. Minimally conscious patients demonstrate inconsistent, but reproducible signs of awareness. Locked-in patients, except for those completely locked-in, often exhibit signs of awareness through small, but reproducible movements. Image adapted from reference.1
80x53mm (300 x 300 DPI)

Behavioral characteristics of patients with disorders of consciousness

Coma

There are no signs of wakefulness - no spontaneous eye opening, even to intense stimulation – and no signs of awareness. Usually it is transient, a few days or weeks, and in rare cases, chronic.

Vegetative state

There are signs of wakefulness, including eye opening and stimulus-induced arousal, but no signs of awareness of oneself or of the environment. The state is considered permanent one year after a traumatic brain injury, or three months after brain damage from lack of oxygen.

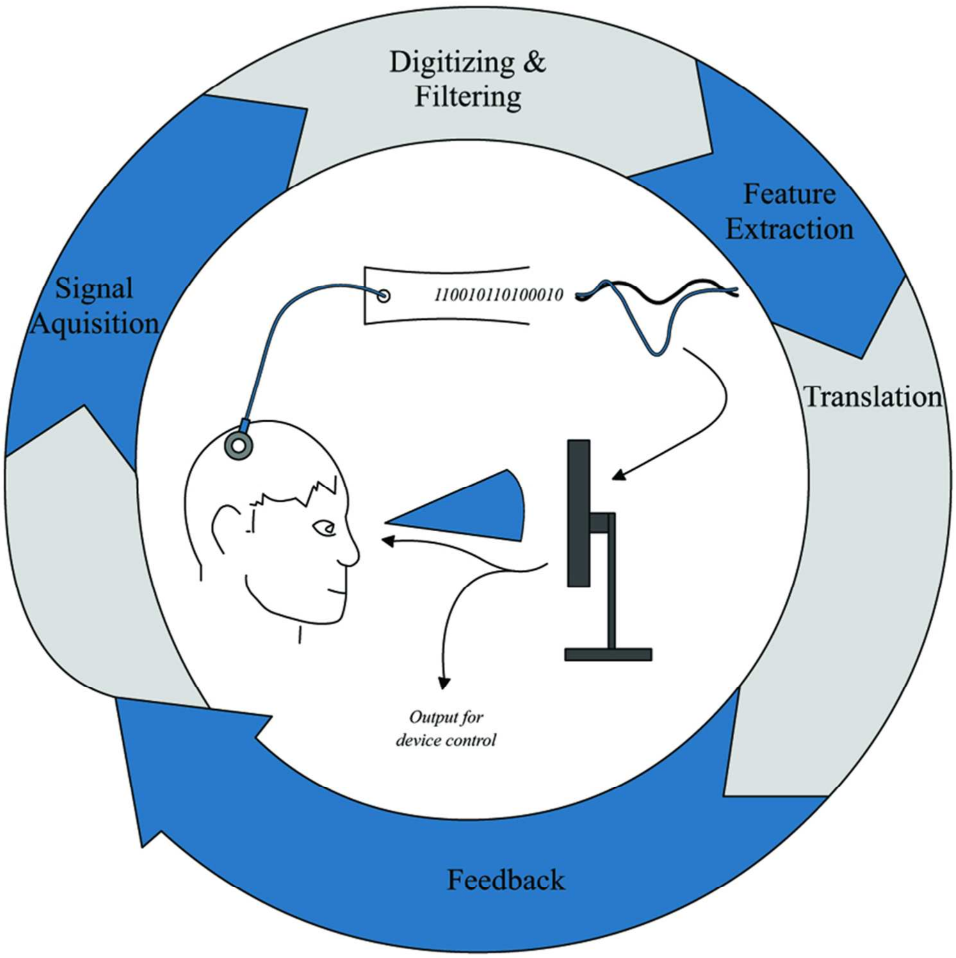
Minimally conscious state

There are signs of wakefulness and inconsistent, but reproducible signs of awareness, including sustained visual pursuit, command following, and intelligible verbalization. It may be chronic or permanent, though no time intervals have been defined.

Locked-in state

Patients are usually aware, but unable to move or speak, and, unless com pletely locked-in, may communicate via small eye movements. In the acute phase, awareness may be impaired.

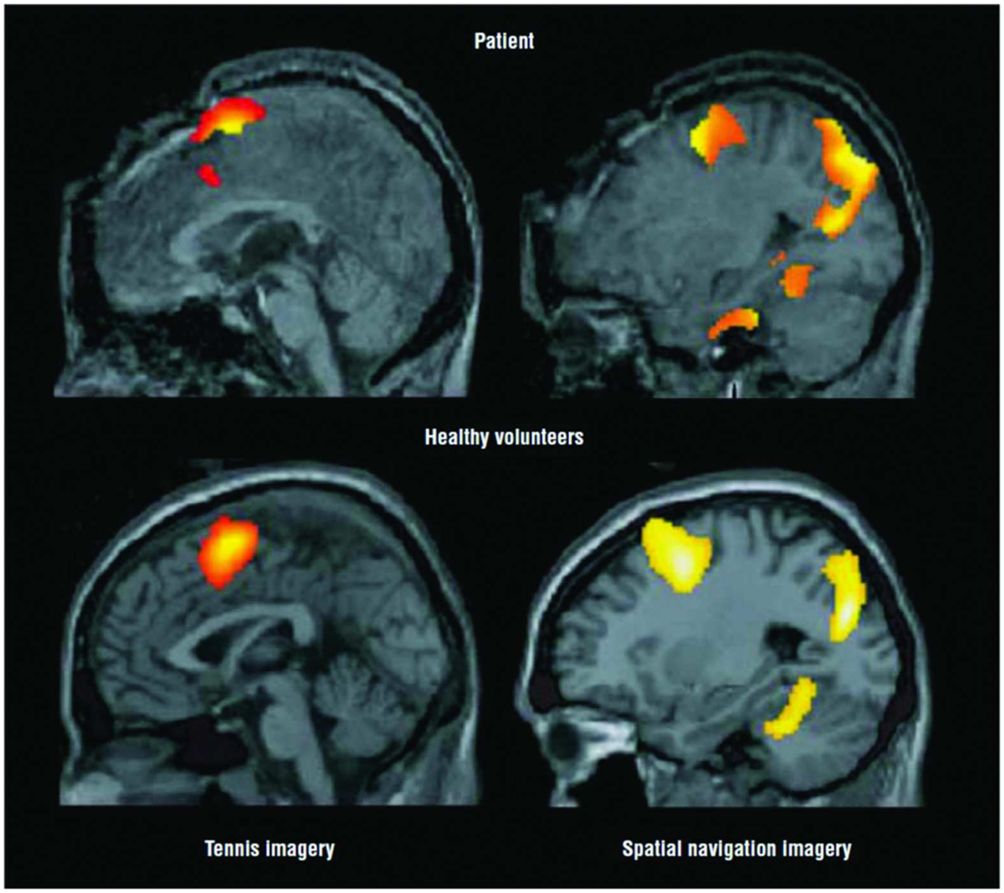
Behavioural characteristics of patients with disorders of consciousness.
72x187mm (300 x 300 DPI)



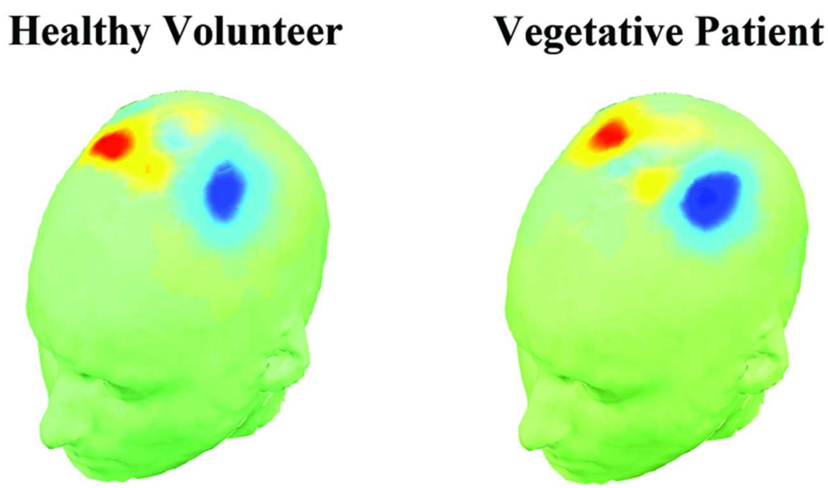
Schematic representation of a BCI system. The BCI cycle starts with the user engaging in a task, in the presence or absence or sensory stimulation. The resulting brain is preprocessed and analyzed for specific features that signal the user’s intent, and translated into a command, which brings about a state change of the BCI system. This is fed-back to the user, for example, through a visual display. This cycle can be repeated iteratively to achieve online communication between the operator and BCI user (courtesy of Andrea Kübler).
80x80mm (300 x 300 DPI)

Functional Neuroimaging Methods	**Advantages**	**Limitations**
FMRI	Non-invasive Global brain coverage High spatial resolution (millimetre's range) Sophisticated analyses methods 1st to demonstrate plausability of communication with patients deemed to be in a VS	High cost Lack of portability Physical impositions (e.g., patient must stay still, and in supine position for an extended period of time) No paramagnetic equipment can be present Noisy Susceptible to movement artifacts Lower temporal resolution than EEG (second's range)
FNIRS	Non-invasive Portable Relatively low cost Nearly noiseless Less sensitive to movement artifacts than fMRI Easier to operate than fMRI No restriction on paramagnetic medical equipment	A relatively new methodolgy; limited experience with BCI applications Limited spatial resolution (~3cm)/especially poor resolution of deep brain structures Some susceptibity to movement artifacts Analyses methods under development
EEG	Non-invasive Portable Relatively low cost High temporal resolution (millisecond's range) Silent No physical impositions (e.g., can be applied in the seated and supine positions, or when the patient is asleep) Vast BCI experience with different patient populations	Limited spatial resolution (~3cm)/especially poor resolution of deep brain structures Susceptible to artifacts from cranial muscles and eye movements The majority of existing paradigms have limited use for DOC patients (but, see Cruise et al. 2011)

Summary of advantages and limitations of fMRI, fNIRS, and EEG for BCI applications for non-responsive patients.
170x136mm (300 x 300 DPI)



Conscious responses to stimuli in a patient who fulfilled all the clinical criteria defining the vegetative state, revealed by fMRI. The bottom panel shows the brain activation in responses of the supplementary motor area (SMA) during tennis imagery, and the parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) during imagery of spatial navigation, in a patient who fulfilled all of the internationally agreed criteria for the vegetative state. These responses were indistinguishable form that of a group of healthy volunteers (n=12). Image reproduced with permission from reference 4 .
80x70mm (300 x 300 DPI)



Conscious responses to stimuli in a patient who fulfilled all the clinical criteria defining the vegetative state, revealed by EEG. The EEG response during a motor imagery task shows clear foci over the hand and toe motor-areas, which are formally identical when compared between a healthy control participant and a vegetative state patient. Image reproduced with permission from reference 2.
80x45mm (300 x 300 DPI)