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Emerging Theory and Practice in Neuroprosthetics

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<i>Ganesh R. Naik, University of Technology Sydney (UTS), Australia</i>	

In this chapter, Ganesh Naik explains the recent advances and applications of neuroprosthetics. Neuroprostheses use electric stimuli to stimulate neural structures, muscles, or receptors in order to support, augment, or partly restore the respective disordered or lost function. The objective is to help the patient to participate in everyday life. The use of a neural prosthesis can improve the quality of life of the person concerned. The future of neuroprosthetics is challenging as well as interesting as it deals with several latest technological advancements that connect both biology and technology together.

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<i>Milan Djilas, INSERM/CNRS/UMPC, France</i>	
<i>Serge Picaud, INSERM/CNRS/UMPC, France</i>	

In this chapter, Djilas and Picaud discuss neuroanatomical and current open issues of the retinal prosthetics, such as implant placement, biocompatibility, electrode design, and safety. They first briefly introduce the neuroanatomical basis for vision and explain how the retina processes visual information. Pathology of the retina and the conditions that cause photoreceptors degeneration and lead to blindness are then given, followed by the main part of the chapter in which authors present an overview of the concept of restoring vision with visual prosthetics. The focus is specifically on retinal prostheses and electrical stimulation parameters used with these devices. Both in vitro and in vivo animal studies from the last decade are surveyed, together with the latest results from human trials conducted in multiple research centres worldwide. In the final section, the authors give their opinion on the future development and perspectives of the retinal prosthetics research.

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Emilia Ambrosini, Politecnico di Milano, Italy

Noelia Chia Bejarano, Politecnico di Milano, Italy

Alessandra Pedrocchi, Politecnico di Milano, Italy

In this chapter, Ambrosini, Bejarano, and Pedrocchi summarize the state of the art of sensors used in Functional Electrical Stimulation (FES) and motor neuroprostheses. Clinical applications of FES provide both functional and therapeutic benefits. To enhance the functionality of FES systems and to improve the control of the activated muscles through open-loop or feedback controllers, solutions to gather information about the status of the system in real time and to easily detect the intention of the subject have to be optimized. These sensors can be classified in two categories: sensors of biological signals and sensors of non-biological signals. Here, the authors report definitions, advantages, and disadvantages for each sensor and also explain guidelines to compare sensors for the design of motor neuroprostheses.

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Emilia Mikołajewska, Military Clinical Hospital No. 10 and Polyclinic, Poland

Dariusz Mikołajewski, Kazimierz Wielki University, Poland & Nicolaus Copernicus

University, Poland

In this chapter, Mikołajewska and Mikołajewski answer the question, how can biomedical engineers be incorporated into research and clinical practice in neuroprosthetics considering the various factors, necessary changes in educational processes, ethical issues, and associated organizational problems? Current models of education and cooperation within interdisciplinary therapeutic teams only concern medical specialists. The development of novel technologies associated with neuroprosthetics and their clinical applications needs and interdisciplinary knowledge, including not only medical sciences, but IT, biomedical engineering, biocybernetics, and robotics. The variability of possible neurological deficits, interventions, and even scales—from nanotechnology up to rehabilitation robots and brain-computer-interface controlled exoskeletons as whole-body neuroprostheses—make this task very difficult.

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In this chapter, Pisotta and Ionta review the hurdles involved in making the Brain-Machine Interfaces (BMIs) a reality. Humans experience and interact with the world through their body. One of the most important features of the human is the interaction between mind and body. Since the original demonstration that electrical activity of the cortical neurons can be employed to directly control a robotic device, the research on the so-called BMIs has impressively grown. For example, current BMIs dedicated to both experimental and clinical studies can translate raw neuronal signals into computational commands to reproduce reaching or grasping in artificial actuators. These developments hold promise for the restoration of limb mobility in paralyzed individuals. Before this goal can be achieved, several hurdles have to be overcome, including developments in real-time computational algorithms and in designing fully implantable and biocompatible devices. Future investigations will have to address the best solutions for restoring sensation to the prosthetic limb, which still remains a major challenge to full integration of the limb into the user's self-image.

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Emilia Mikołajewska, Military Clinical Hospital No. 10 and Polyclinic, Poland

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Emilia Mikołajewska, Military Clinical Hospital No. 10 and Polyclinic, Poland

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Tomasz Wolak, Institute of Physiology and Pathology of Hearing, Poland

In this chapter, Mikołajewska et al. investigate the available opportunities and limitations in usage of Assistive Technology (AT) devices for elderly people, including medical, technical, psychological, societal, ethical, and legal issues. Recent demographic prognoses show tendencies toward significant increase in number of elderly people, especially in developed countries. This makes geriatric therapy, rehabilitation, and care difficult, especially with maintaining the highest quality of life and independence in activities of daily living as long as possible. Lack of specialized personnel and financial shortages may cause increased application of Assistive Technology (AT) and associated control devices. The most advanced current devices for diagnosis, communication, and control purposes are perceived Brain-Computer Interfaces (BCIs). BCIs are regarded as novel solutions offering another breakthrough in everyday life, care, therapy, and rehabilitation in patients with severe sensory and neuropsychological deficits. However, particular issues in the area of BCIs use in elderly people should be emphasized, including influence of neurodegenerative disorders accompanied with secondary changes resulting from other medical problems (e.g. heart diseases, hypertension, diabetes mellitus, and osteoporosis), co-occurrence of various drug therapies, etc.

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Younghak Shin, Gwangju Institute of Science and Technology, South Korea

Seungchan Lee, Gwangju Institute of Science and Technology, South Korea

Heung-No Lee, Gwangju Institute of Science and Technology, South Korea

In this chapter, Soogil Woo et al. review the research trends for wireless Brain-Computer Interface (BCI) systems, as well as their current and anticipated applications. Wireless BCI systems have clear advantages, when compared to wired BCI systems, in that they have simpler shapes and can be convenient and portable devices. Recent wireless BCI applications attempt to help people live more conveniently in many areas of life: medical engineering, rehabilitation, and everyday life.

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Monzurul Alam, The Hong Kong Polytechnic University, Hong Kong

Jufang He, The Hong Kong Polytechnic University, Hong Kong & City University of Hong Kong, Hong Kong

In this chapter, Alam and He discuss available therapies for the rehabilitation of Spinal Cord Injury (SCI) paraplegics and some new potential interventions that still require clinical tests. They also propose brain-machine-spinal cord interface as a future neuroprosthesis following motor complete SCI. Regaining lower-limb functionality such as walking is one of the highest priorities among all the disabilities of paraplegics following SCI. Though the ultimate recovery would be repairing or regenerating new axons across the spinal lesion (potentially by stem cells or other transplants and neurotropic factors), challenges to achieve this as well as recent technological advancements demand the development of new neuroprosthetic devices to restore such motor functions following the injuries.

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Christoph Guger, Guger Technologies, Austria

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Gernot Müller-Putz, Graz University of Technology, Austria

Steven Laureys, University of Liege, Belgium

Andrea Kübler, Universität Würzburg, Germany

In this chapter, Guger et al. discuss current methods and problems associated with Disorders of Consciousness (DOC) and highlight the possible solutions to the same. Many patients with DOC are misdiagnosed for a variety of reasons. These patients typically cannot communicate. Because such patients are not provided with the needed tools, one of their basic human needs remains unsatisfied, leaving them truly locked in their bodies. This chapter first reviews current methods and problems of diagnoses and assistive technology for communication, supporting the view that advances in both respects are needed for patients with DOC. The authors also discuss possible solutions to these problems and introduce emerging developments based on EEG (Electroencephalography), fMRI (Functional Magnetic Resonance Imaging), and fNIRS (Functional Near-Infrared Spectroscopy) that have been validated with patients and healthy volunteers.

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Catherine Best, University of Stirling, UK

Brian O'Neill, Graham Anderson House, UK

Alex Gillespie, London School of Economics, UK

In this chapter, Best, O'Neill, and Gillespie review the use of assistive technology in health and social care for people with cognitive impairment. This review updates their previous reviews on this topic and reflects on how their conceptualization of Assistive Technology for Cognition (ATC) in terms of function (reminding, alerting, micro prompting, distracting, storing, displaying, navigating, and biofeedback), as opposed to the type of technology (mobile phone, desktop computer, etc.), and fits with recent developments in this field. The authors highlight the growing number of context-aware prompting devices and the move to train people with cognitive impairment to use everyday technology such as mobile phones. They also make a distinction between ATC, which augments or supplants cognitive functions, and outline avenues for future research.

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Rüdiger Rupp, Heidelberg University Hospital, Germany

Martin Rohm, Heidelberg University Hospital, Germany

Matthias Schneiders, Heidelberg University Hospital, Germany

In this chapter, Rupp et al. provide an overview of the current state of the art of Brain-Computer Interface (BCI) controlled upper-extremity neuroprostheses and describe the challenges and promises for the future. For individuals with tetraplegia, restoring limited or missing grasping function is the highest priority. In patients with high Spinal Cord Injury (SCI) and a lack of surgical options, restricted upper extremity function can be improved with the use of neuroprostheses based on Functional Electrical Stimulation (FES). Grasp neuroprostheses with different degrees of complexity and invasiveness exist, although few models are available for routine clinical application. Hybrid systems combining FES with orthoses hold promise for restoring completely lost upper extremity function. Novel user interfaces integrating biosignals from several sources are needed to make full use of the many degrees of freedom of hybrid neuroprostheses. Motor Imagery (MI)-based BCIs are an emerging technology that may serve as a valuable adjunct to traditional control interfaces.

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Wei-Yen Hsu, National Chung Cheng University, Taiwan

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About the Contributors

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* * *

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Monzurul Alam received his PhD in Neuroprosthetics from The Hong Kong Polytechnic University and is currently working as a postdoctoral fellow at Dr. Edgerton's lab, University of California Los Angeles (UCLA). Both his PhD and postdoctoral research have been focused on Spinal Cord Injury (SCI) rehabilitation in rodent models. Electrophysiology, pharmacology, and electrical stimulation are the common techniques applied. Dr. Alam's major research interest is to understand the neural mechanisms underlying the recovery after injuries of the central and peripheral nervous system. He also applies modern engineering techniques to utilize this neural system for prosthetic applications.

Emilia Ambrosini graduated cum laude in Biomedical Engineering in 2007 and obtained a PhD Degree cum laude in Bioengineering in 2011 from Politecnico di Milano. In 2009, she was a visiting PhD student at the Control System Group of the Technische Universität of Berlin. Since March 2011, she is a Research Fellow at Neuroengineering and medical robotics Laboratory (NearLab, www.biomed.polimi.it/nearlab), and she was involved in the European project MUNDUS (FP7 ICT- 2009.7.2). Her research interest is about the design and clinical translation of safe, simple, and immersive devices based on the integration of functional electrical stimulation and robotic systems for the rehabilitation and the daily life assistance of neurological patients. She is also interested on the assessment of neuroplasticity. She is co-author of 11 papers in peer-reviewed international journals.

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Noelia Chia Bejarano received her Master of Science degree in Telecommunications Engineering in 2012 from the University of Seville, Spain. Prior to graduating, Noelia worked as a research assistant in the Electronic Engineering department at the University of Seville, and in 2009, she won a grant for a research internship at the Optics Institute "Daza de Valdés" of the Spanish National Research Council (CSIC), where she co-authored an article on Spectral Optical Coherence Tomography (sOCT). From 2011 to 2012, she was an exchange student at Politecnico di Milano, and a visiting student at the Neuroengineering and Medical Robotics Laboratory (NearLab). Since November 2012, Noelia is a PhD student in Bioengineering at Politecnico di Milano, where she is currently developing a rehabilitation system for neurological patients and older adults based on inertial sensors and functional electrical stimulation.

Catherine Best has a BSc in Psychology and Neuroscience from the University of Manchester and a PhD from the University of Edinburgh, Division of Psychiatry. After graduating, she worked in services for people with long-term mental health conditions for 6 years. For the last 10 years, she has been involved in research in the field of health and social care. Her research interests are in the neuropsychology of neurodevelopmental and psychiatric disorders, interventions to promote independence well-being for people with long-term health problems, and assistive technology for cognition. Her methodological expertise and interests are in the conduct of systematic literature reviews and conducting research in vulnerable/difficult to recruit populations such as young people with developmental disorders and people with long-term mental health problems.

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Milan Djilas obtained a Dipl. Ing. degree in Electrical Engineering from the University of Belgrade in Serbia, a M.Sc. degree in Biomedical Engineering from the University of Aalborg in Denmark, and a Ph.D. degree in Neural Prosthetics from the University of Montpellier II in France. The topic of his Ph.D. was using implantable neural prosthetics for restoring limb movement in individuals with paralyzed limbs. He was a postdoctoral research fellow at the Vision Institute in Paris, working with Dr. Picaud on the development of high-resolution retinal prosthetics to restore vision to the blind. He is currently an advanced consultant in Altran Switzerland, consulting other companies in the life sciences and healthcare industries.

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Rainer Goebel (1964), professor of Cognitive Neuroscience, studied psychology and computer science in Marburg (Germany, 1983-1988). He received his PhD at the Technical University of Braunschweig (Germany, 1994). From 1995-1999, he was Postdoc at the Max Planck Institute for Brain Research in Frankfurt/Main (Germany). In 2000, he was appointed full professor at Maastricht University (Faculty of Psychology and Neuroscience, The Netherlands). Since 2005, he has been director of the Maastricht Brain Imaging Centre. From 2006-2009, he was chair of the Organization for Human Brain Mapping. Since 2008, he has been team leader of the neuromodeling and neuroimaging group at the Netherlands Institute for Neuroscience of the Royal Netherlands Academy of Arts and Sciences. His research includes high-resolution functional imaging of the visual system, artificial large-scale columnar-level neural network models of visual cortex, as well as development of hemodynamic brain-computer interfaces (including neurofeedback) and of new analysis methods for neuroimaging data.

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Jufang He obtained a B.Eng. and M.Eng. degree in Engineering at the Harbin Institute of Technology, a Doctoral Degree in Medical Science at the University of Tokushima, and a second Doctoral Degree in Engineering at the University of Tokyo, Japan. Before joining the City University of Hong Kong in September 2013, Prof. He had worked at Riken (Japan), University of Tokushima, and Advanced Research Laboratory of Hitachi Ltd. for 5 years, and The Hong Kong Polytechnic University (PolyU) for 15 years. Prof. He combines electrophysiological, anatomical, and engineering approaches to answer fundamental questions of hearing, and learning and memory. Besides Neurobiology, Prof. He has developed an electronic “bat ear” for people with visual impairments and a “motolink” for bypassing the spinal cord injury. Prof. He is directing a collaborative team between CAS and CityU for developing a memory drug.

Lizette Heine (1988) is a PhD student at the coma science group at the University of Liege (Belgium). In 2010, she finished her bachelor in biological psychology at Maastricht University (The Netherlands). During her master in Neuropsychology at the same institution, she focused under the supervision of Dr. Bettina Sorger and Prof. Dr. Rainer Goebel on resting state and active imagery paradigms using Functional Magnetic Resonance Imaging (fMRI) and Functional Near-Infrared Spectroscopy (fNIRS). Since October 2012, she has worked as a research fellow in biomedical sciences at the coma science group under the supervision of Prof. Dr. Steven Laureys. Her work mainly focuses on assessment of residual cognitive processing in non-communicating patients through the combination of fMRI, diffusion-weighted imaging, and clinical neuropsychological testing.

About the Contributors

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Andrea Kübler is Professor of Psychological Intervention at the University of Würzburg. She received Master Degrees in Biology and Psychology and her PhD in Biology. During her PhD, she developed a BCI on the basis of slow cortical potentials for communication with locked-in patients. She is an expert in Neurofeedback and training locked-in patients with different BCI. Currently, she is investigating how affective states and motivation influences BCI performance, what predicts BCI performance, and how BCI can be brought to the patients' bedside. She is further investigating how BCIs can be used for the detection of consciousness in non-responsive patients and for cognitive rehabilitation after stroke. Other research interests are addiction and eating disorders, quality of life and coping with disease, and intervention for children and adolescents with sleeping disorders. She has numerous publications in the BCI field and holds four national and international grants for research on BCI.

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Adrian M. Owen is currently the Canada Excellence Research Chair (CERC) in Cognitive Neuroscience and Imaging at the University of Western Ontario, Canada. His work combines structural and functional neuroimaging with neuropsychological studies of brain-injured patients. His most recent work, reported in the journals *Science* (2006), *The New England Journal of Medicine* (2010), and *The Lancet* (2011) has shown that functional neuroimaging can reveal conscious awareness in some patients who appear to be entirely vegetative, and can even allow some of these individuals to communicate their thoughts and wishes to the outside world. These findings have attracted widespread media attention on TV, radio, in print and online, and have been the subject of several TV and radio documentaries. Dr. Owen has played multiple editorial roles including 8 years as Deputy Editor of *The European Journal of Neuroscience*. Since 1990, Dr. Owen has published over 200 articles and chapters in scientific journals and books.

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Chapter 10

Brain–Computer Interfaces for Assessment and Communication in Disorders of Consciousness

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ABSTRACT

Many patients with Disorders of Consciousness (DOC) are misdiagnosed for a variety of reasons. These patients typically cannot communicate. Because such patients are not provided with the needed tools, one of their basic human needs remains unsatisfied, leaving them truly locked in to their bodies. This chapter first reviews current methods and problems of diagnoses and assistive technology for communication, supporting the view that advances in both respects are needed for patients with DOC. The authors also discuss possible solutions to these problems and introduce emerging developments based on EEG (Electroencephalography), fMRI (Functional Magnetic Resonance Imaging), and fNIRS (Functional Near-Infrared Spectroscopy) that have been validated with patients and healthy volunteers.

INTRODUCTION

The clinical care and rehabilitation approaches involving patients diagnosed with disorders of consciousness (DOC) are of great medical and social importance. The progressive increase in the number of surviving patients and their increasing life expectancies, in all industrialized countries, reflects the advancement of knowledge and techniques in the field of reanimation, as well as improved quality of care. An accurate early diagnosis is indispensable to develop early and effective standards of care, appropriate to an individual patient's condition. The clinical diagnosis of these patients is a major challenge because of the very fine line between the Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS; Laureys et al., 2010), characterized by preserved arousal in the absence of behavioral signs of awareness, the Minimally Conscious State (MCS),

with non-reflexive albeit inconstant purposeful behaviors, and the Locked-In Syndrome (LIS), in which consciousness is fully preserved (Giacino et al., 2002). Recent work identified two groups within this patient population - those who show higher-order signs of consciousness (*e.g.*, command following, intelligible verbalization, and non functional communication; *i.e.* MCS plus) versus those who show only low-level signs of consciousness (*e.g.*, visual pursuit of a salient stimulus, noxious stimulation localization, appropriate emotional response; *i.e.* MCS minus) (Bruno et al., 2011; Bodart et al., 2013).

Despite the efforts already made to improve the instrumental diagnosis, differential diagnosis between different patients with an altered state of consciousness is eminently clinical and based on a list of items that the patient is unable to perform. The LIS is a term introduced by Plum and Posner to describe a neurological condition

of quadriplegia and anarthria associated with ventral pons infarction (Plum & Posner, 1966). The American Congress of Rehabilitation Medicine defined the LIS as: i) the presence of sustained eye opening, ii) the preservation of cognitive skills, iii) a severe hoarseness or hypophonia iv) quadriplegia or quadriparesis, and v) a primary mode of communication using eye movements or blinking (American Congress of Rehabilitation Medicine, 1995). The main etiology of LIS is stroke (Patterson & Grabois, 1986). The diagnosis of this condition is particularly challenging because patients cannot communicate by the usual means. These patients are fully conscious but completely or almost completely unable to move and speak, so they can easily be mistaken for VS patients.

Evidence-based medicine (EBM) has been defined as the integration of current best evidence with clinical experience and patients' values and preferences in clinical decision-making process (Brownson et al., 2012). With the introduction of EBM, the clinicians are exhorted to consider all three factors in the process to foster the evidence-based-decision-making (EBDM) in public health. These concepts appear of utmost relevance when dealing with disorders of consciousness characterizations, which entail a broad spectrum of entities that are often misdiagnosed.

In this context, the development of brain-computer interface (BCI) tools, as well as other *paraclinical* instruments and methods, can facilitate the differentiation of these clinical states. BCIs are devices that allow users to communicate directly by means of brain activity. Recently, BCIs have become much more practical and flexible, due to advances such as dry electrodes, high-impedance amplifiers, better interfaces (Kaufmann et al., 2013a), and improved testing with patients in clinical settings (Zickler et al., 2011). Hence, BCIs are becoming useful to broader groups (Guger et al., 2012; Wolpaw and Wolpaw, 2012; Allison et al., 2013).

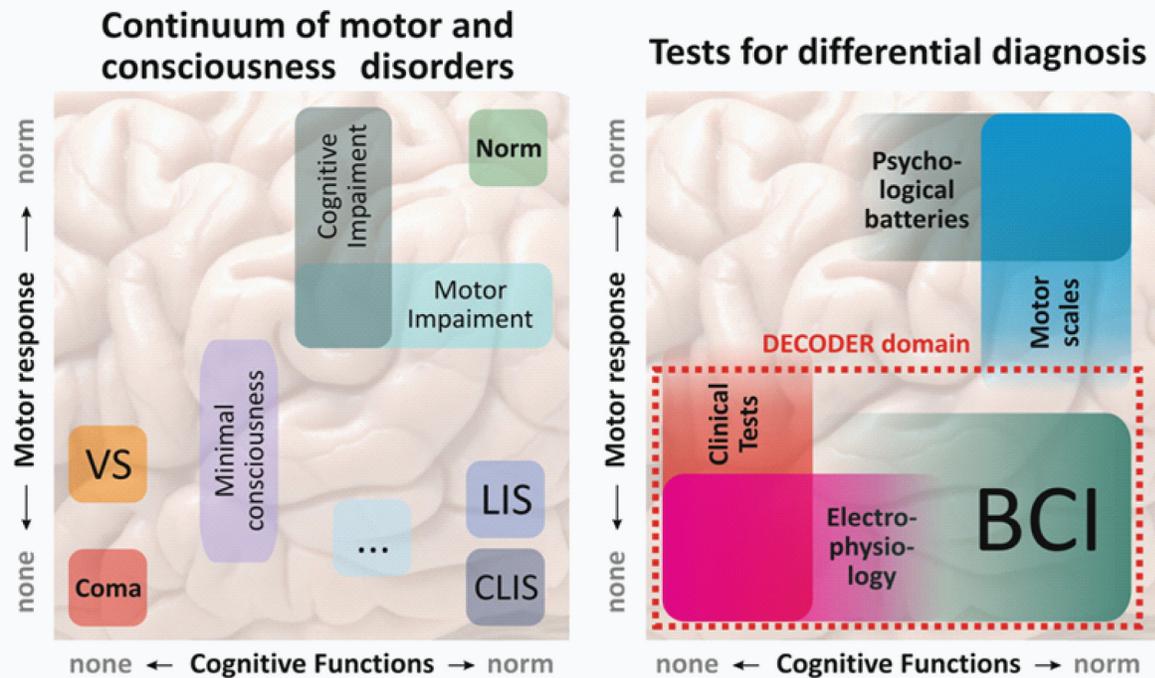
The main objective of this chapter is to show how BCI technology is becoming useful to DOC patients. The two main functions are for communication, which has been well established for BCIs, and detection of consciousness, which is relatively unexplored. We will first review background material showing that conventional methods need improvement, and then introduce EEG methods. This sets the stage to present new research studies through the European Commission (EC) research project DECODER (www.decoderproject.eu), using EEG, fMRI and fNIRS to show that BCI technology can supplement conventional methods.

BACKGROUND

Forty-three percent of patients diagnosed as being in the VS are reclassified as (at least) minimally conscious when assessed by expert teams (Schnakers et al., 2009). Other DOC patients might appear non-communicative through standard clinical testing, but could be able to communicate with newer methods. Furthermore, some DOC patients have transient periods of relative wakefulness, but remain unaware of their surroundings. The European project DECODER (see Figure 1) aimed at using BCI technology to identify DOC patients who might be able to communicate through newer, BCI based technologies.

One recent study showed that patients identified as being in a vegetative state VS were not only consciously aware, but could answer yes or no questions (Monti et al., 2010). This work demonstrates that some patients meet all behavioural criteria for VS, but nevertheless have covert awareness. Some research to assess cognitive activity in DOC patients relies on fMRI. Functional MRI can be very powerful but also entails major limitations, as discussed in the next section.

Figure 1. A graphical depiction of how the DECODER project could facilitate DOC assessment



Functional MRI to Assess Conscious Awareness and Communicate with Patients with DOC

Overview

Although EEG-based systems are portable, and far less expensive than fMRI, fMRI has also been used successfully to develop a BCI system for patients with disorders of consciousness (DOC). Functional MRI measures the changes in blood oxygenation level of the brain, known as haemodynamics (Ogawa et al., 1993; Kwong et al., 1992). fMRI has several strengths for BCI applications, including its non-invasive nature, brain coverage and excellent spatial resolution (in the millimeter range).

Owen and colleagues (2006) employed an fMRI-based mental imagery paradigm to assess command-following in a patient who had been diagnosed behaviourally as in the 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 functional activation in the expected 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 (Boly et al., 2007; Owen et al., 2006). The patient’s functional activation was statistically robust, reproducible, task-appropriate, and sustained over

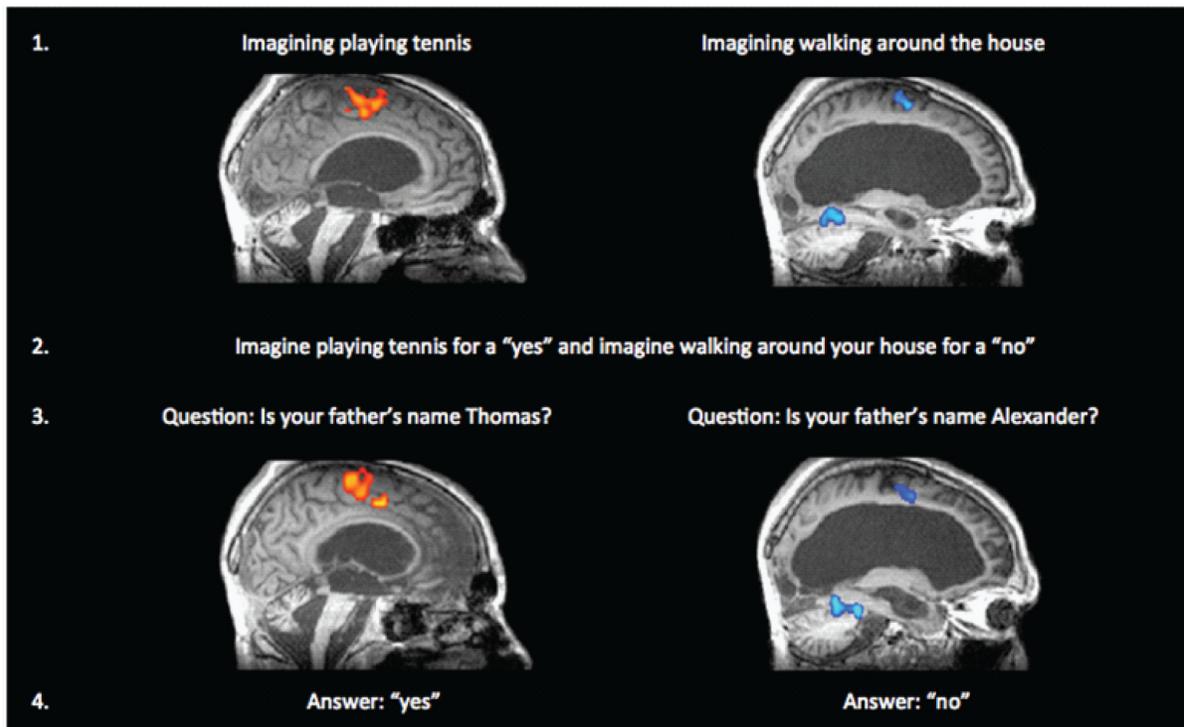
long time-intervals (30 seconds), allowing Owen and colleagues (2006) to conclude that she was responding to the commands by performing the imagery tasks in the absence of any overt action, and thus, that she was falsely diagnosed as being in the VS, albeit correct according to behavioural measures.

Using fMRI to Achieve Binary Communication with DOC Patients

Monti et al. (2010) extended this approach to demonstrate that fMRI could also be used to *communicate* with a behaviourally non-responsive

patient who was assumed to be in the 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 Owen et al., 2006). Following five autobiographical questions (e.g., “Is your father’s name Thomas?”), the answers that were decoded from the brain activity matched the factually correct answers, which were unknown to the experimenters at the time (Figure

Figure 2. The top panel (1 - 2) shows the patient’s brain activation when he is imagining playing tennis (left), and when he is imagining walking around his house (right). The patient’s brain activity was indistinguishable from that of the healthy controls performing the same tasks. The bottom panel (3 - 4) shows the patient’s brain activity when he was instructed to use these mental imagery tasks to convey either the word ‘yes’ or ‘no’, in response to being asked binary (‘yes’/‘no’) questions. The patient’s brain activation could unequivocally decode the answers to several autobiographical questions. The responses derived from the patient’s brain activity were subsequently corroborated as factually correct by the patient’s family.



2). This study demonstrated that the presence of voluntary, reliable, and sustained brain activity in response to a command could be used as a proxy for physical behaviour, such as movement or speech, to facilitate communication with non-responsive participants (Owen and Coleman, 2008).

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. Several other factors, however, may also explain these findings. First, this technique might lack sensitivity, and thus failed to show activation in patients who might have been engaged in the task (Bardin et al., 2011). 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 (Rossini et al., 2004; Gsell et al., 2000). 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 (Monti et al., 2013). Finally, in some patients, functional re-organization of the brain following the injury may have produced highly atypical patterns of fMRI activation, which may be impossible to interpret.

Discussion and Future Directions

Multi voxel pattern analysis (MVPA), an fMRI analysis technique that is highly sensitive to the information content in the neural signal, may provide a solution to some of these issues. Traditional univariate fMRI analyses average across activations in a brain region, and compare overall changes in signal strength between different types of conditions (Friston et al., 1995). 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 (deCharms, 2007; 2008), which could not be disentangled with univariate methods (Haynes and Rees, 2006). By dissociating several mental states or responses elicited by a single command (Chadwick et al., 2010; Kay et al., 2008), MVPA also has the potential to expand communication from binary responses to multiple-choice answers. For example, while further in the future, MVPA could lead to tools that can help ask patients to express how much pain they feel on a sliding scale from 1-10 by imagining the appropriate number.

MVPA methods can also be applied in real-time (Caria et al., 2012; Sitaram et al., 2011; Lee et al., 2009; LaConte et al., 2007), and present exciting possibilities for communication without any 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 due to physical reasons. For example, patients may experience difficulty lying supine for long periods of time. Moreover, VS patients may become exhausted easily and are very likely to exhibit a very short attention span.

In summary, fMRI has great strengths for BCI applications, including its non-invasive nature, global brain coverage, and excellent spatial resolu-

tion of specific brain structures. However, fMRI 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, refrain from any minor movement, and be able to cope with the loud noise of the fMRI scanner), render this technology unlikely to provide the ultimate communication solution that DOC patients require in real life situations. Electroencephalography and fNIRS are not susceptible to such caveats, and provide exciting opportunities to promote and further develop the insight gained with fMRI.

Conventional EEG Methods

Unlike fMRI, EEG is easy to set up, portable, widely available and inexpensive. EEG is one of the most important neurophysiological methods to assess cognitive functions (*e.g.*, attention, language, etc.) in humans. These features make it practical for bedside testing. EEG also can measure brain activity with excellent temporal resolution. One common method of analyzing EEG data is to extract event-related potentials (ERPs) from the recorded EEG. An ERP is a specific brain pattern that is time-locked to a specific event, such as a flash, tone, or movement (Luck, 2005). In general, ERPs reflect the synchronous activity of postsynaptic potentials produced by the parallel firing of cortical pyramidal neurons during information processing (Peterson et al., 1995). In healthy participants, those reactions are elicited reliably and are well-studied. Based on this, they can also serve as important indicators of cognitive function in severely disabled patients with DOC (Kotchoubey et al., 2005, D'Arcy et al., 2011).

EEG can indeed be useful for assessing cognitive state and for communication. One recent

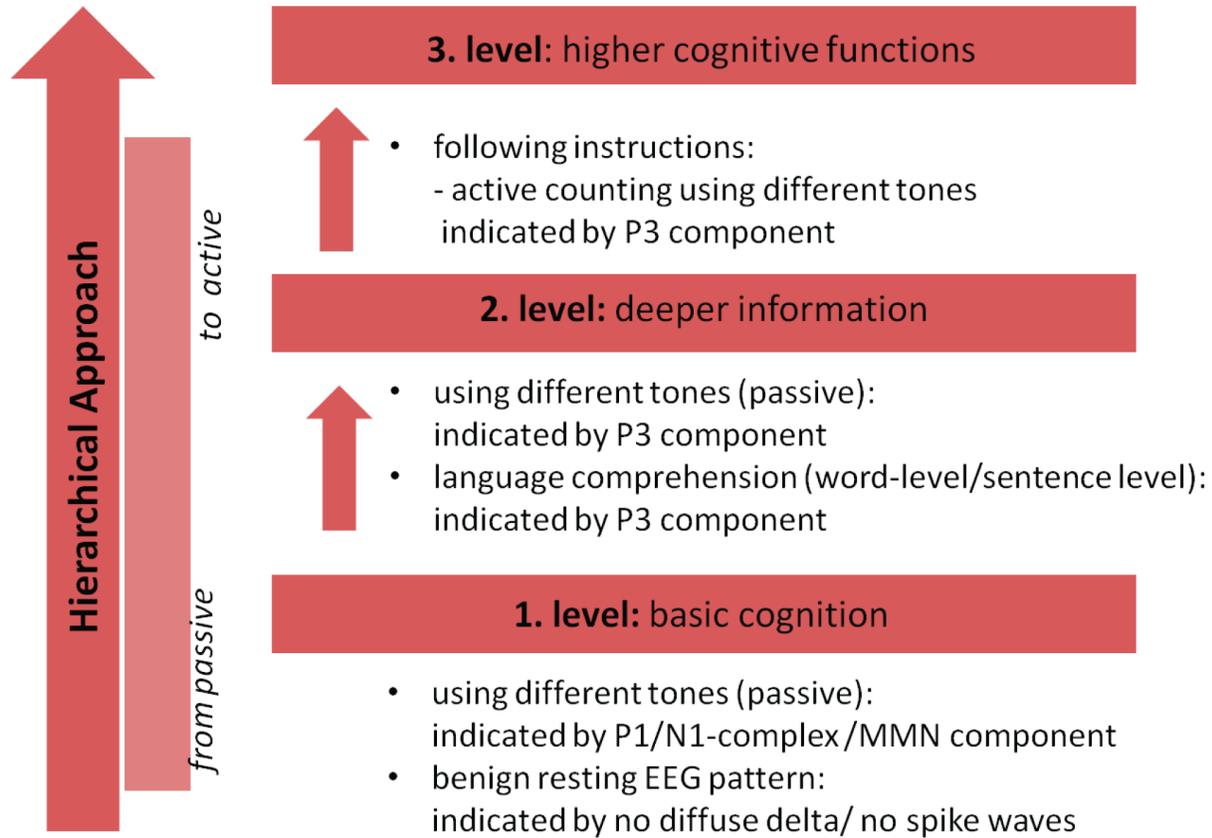
study found that 3 of 16 patients (19%), who were classified as VS and totally unresponsive behaviourally, could consistently produce specific EEG patterns to two different commands (Cruse et al., 2011). These results show that EEG methods could help identify VS patients who might be able to communicate with an EEG-based BCI. However, developing practical and reliable tools in field settings entails many challenges such as patients' low attention span, demanding set-up, and electrically noisy environments.

The Hierarchical Approach and Relevant ERP Components

The hierarchical approach is regarded as the most effective way to examine cognitive functioning in DOC patients (Kotchoubey et al., 2005; Kübler and Kotchoubey, 2007; Owen et al., 2005). Figure 3 depicts the interplay of the three suggested levels of the hierarchical approach investigating different cognitive functions underlying consciousness. Different EEG paradigms, each of which elicits specific ERP components, are associated with each of the levels.

The first level includes the assessment of basic cognitive functions. These functions may be completely unconscious, but this level is critical before moving to the next level. Within the first level, paradigms test the patient's sensory and automatic cognitive information processing capacities, which are reflected in the ERP components P1/N1 (sensory input) and the mismatch negativity (MMN). Typically, the MMN is elicited by a rare stimulus, called deviant, that differs from the frequently-occurring stimuli, called standards, in one or more physical parameters such as duration, intensity, frequency or location (oddball paradigm; Näätänen et al., 2004; Schröger and Wolff, 1996; Jacobsen and Schröger, 2003). The MMN is in-

Figure 3. Hierarchical approach with three different levels of cognitive processing and their respective EEG/ERP indicators



terpreted as an index of a mismatch between the actual stimulus and the memory trace of physical or abstract environmental regularities. Thus, it appears in response to a violation of simple rules or expectations (for review, see Näätänen et al., 2007). The important characteristic of this violation detection is the high level of automaticity. MMN paradigms can be used successfully in non- and low-responsive patients (Kane et al., 2000; Guérit, 2005) because MMNs do not depend on the actual cognitive state of a patient (*e.g.*, fatigue, monotony) and the daily fluctuations of arousal (Kotchoubey et al., 2003). Therefore, the MMN is a good predictor toward a positive or negative outcome of comatose patients (*e.g.*, Fischer et al., 1999, see also meta-analysis by Daltrozzo et al.,

2007) as well as for the improvement of VS patients (Kotchoubey et al. 2005; Wijnen et al., 2007).

The second level can reveal deeper information processing that indicates, though does not prove, conscious intentional states. One way to test this level is to assess language related processes, reflected in the N400 ERP component (*e.g.*, Kutas & Hillyard, 1980). The N400 is strongly correlated with semantic manipulation (Hagoort, 2005; Kutas & Federmeier, 2011; Sitnikova et al., 2002) and is distributed over centro-parietal areas. The semantic manipulation can be achieved on the word level by presenting word pairs which are related (mountain-valley) or unrelated to each other (place-bravery; Hagoort et al. 1996) and on the sentence level by presenting sentences with

correct word endings (“The eel is aquatic.”) and incorrect word endings (“The eel is a bird.”; Connolly et al. 1992). Thus, a more pronounced N400 component for unrelated/incorrect conditions compared to the related/correct conditions indicates the ability of low- and non-responsive patients to process complex language information (Kotchoubey et al., 2002). Recently, research also showed that correctly and falsely negated sentences (birds cannot speak vs. birds cannot fly) elicit an N400 of a different amplitude (Herbert and Kübler, 2011). As negation requires cognitive as opposed to automatic processing, this paradigm may be regarded as transitory between the second and the final level.

Finally, the third level includes higher cognitive functions (*e.g.*, selective attention, instruction understanding). Only this level can reveal strong indication of conscious awareness. One ERP component important for this and the previously described second level is the P3 (or P3b). The P3, like the MMN, is often investigated in the context of the oddball paradigm (Duncan-Johnson & Donchin, 1977). The P3 can be elicited without an active instruction, especially to stimuli of particular significance, like a subject’s own name (Fischler et al., 1987, Kotchoubey et al., 2005). However, the P3 increases substantially when subjects are instructed, for example, to count a rare stimulus in a sequence containing frequent and rare stimuli (Lang et al., 1997). Thus, passive P3 paradigms indicate the level two in the hierarchical approach, whereas active P3 paradigms reflect the third level. These paradigms may serve as a battery for the assessment of the level of consciousness (BAC). The following section presents recent research that shows the usage of this hierarchical approach.

CHALLENGES AND ISSUES WITH EEG-BASED METHODS

The previous section demonstrated that, despite substantial research and development, conventional tools for assessing DOC are inadequate. This section discusses dominant issues, methods and paradigms in EEG-based assessment of consciousness. We discuss some limitations of current methods based on interviews and empirical work. Next, we address problems with conventional analysis methods with single subjects and single trials.

Requirements for an EEG-Based Diagnostic Battery for Patients with DOC

Above in this chapter, the major problem of misdiagnosis in DOC patients was largely discussed from the point of view of neuroscience and the results of neuroimaging research. However, the perspective of practicing clinicians is also of importance. We performed a study to assess clinicians’ views regarding current diagnostic procedures and possible improvements. In the past years, studies have repeatedly indicated a high proportion of misdiagnoses in patients in minimal conscious (MCS) and vegetative state (VS) (Schnakers et al., 2009). Thus, diagnosis in such low or non-responsive states needs to be improved, and ongoing research aims at developing diagnostic means based on imaging and electrophysiological techniques. Event-related potentials (ERP) have been shown to be a suitable tool to complement clinical assessment and to detect residual cognitive functions (Kotchoubey et al., 2002). However, such tools have to meet the requirements of physicians in the field and must be developed in close collaboration with

these practitioners, who are the target user group for such an EEG or imaging based diagnostic battery. Following a user-centered approach in which a product is developed in an iterative process between users and developers (*e.g.*, Zickler et al., 2011; Holz et al., 2012; Kübler et al., 2013), nine semi-structured interviews were conducted with representatives from acute care clinics (ACC, 4) and neurological rehabilitation centers (NRC, 5) across Germany.

Interviewees were five medical directors, two chief physicians and two senior physicians. They were told about the development of a new EEG-based diagnostic battery based on auditory ERPs. The interviews covered three main topics: current diagnostic procedures, weaknesses of the current process and expectations concerning a new diagnostic battery. All interviews were recorded and transcribed. Answers to each question were grouped into clusters and counted (Erlbeck & Kübler, 2013).

In general, results supported the hypotheses that clinicians agree that current procedures need improvement. For clarity, answers of ACCs and NRCs will be presented together unless otherwise noted.

Current Procedures

A diagnosis in ACCs is made rather quickly within few hours. NRCs acknowledge the diagnosis provided by the referring ACC but review it on admission of the patient. A diagnosis is regularly checked on an hourly (ACCs), daily or weekly (NRCs) basis depending on the status and medical history of the patient. When making a diagnosis, physicians primarily rely on the clinical assessment, meaning the observation of reactions to auditory, sensory and visual stimuli. All institutions apply EEG, especially in comatose, VS and MCS patients. One institution (NRC) also utilizes measurements of evoked potentials. In some cases, CT (n=6) or fMRI (n=4) are also used. The Glasgow Coma Scale is administered

in six, the Barthel Index in five and the Coma Recovery Scale revised (CRS-r) in two institutions. Seven institutions consider their diagnosis to be of primary importance for treatment decisions and future therapeutic processes. Two institutions (NRC) consider the diagnosis to be important but put a greater focus on prognosis and treatment.

Weaknesses in the Current Procedures

Results in the current diagnostic process partially depend on experience and observational skills of the responsible physician (n=5). Therefore, there is interest in a stronger focus on different aspects of diagnostics in the education of becoming a neurologist (n=3). Another critical issue is the lack of methods to estimate the further development of patients in terms of regaining consciousness or rehabilitative progress (n=3). Furthermore, a lack of sufficient resources to apply imaging techniques was mentioned (n=3). Finally, the consideration for psychological matters and cognitive performance (as the entity that makes us humans) is considered insufficient in neurological diagnostics (n=2).

Requirements and Expectations

A general interest in applying a new, more reliable diagnostic tool was evident in many institutions (one ACC, five NRCs). Three representatives from ACCs could not imagine using it in their institutions but consider it interesting, particularly for therapeutic institutions such as NRCs. All interviewees named reliability and validity as mandatory. Additionally, the tool must not be affected by disturbances typical in a medical environment (n=6) and must be practical in terms of time, personnel, financing and the setup (n=7). Respondents also mentioned that the amount of resources available to invest will largely depend on the benefit of the resulting output (n=4). Taking into account the weaknesses of the current

diagnostics, the most relevant expectations are the prognostic value of the results (n=7) and a support in therapeutic decision-making (n=5). Thus, the output is expected to be accurate in terms of a selective differentiation between various diagnoses and prognoses.

Overall, a correct diagnosis is vital for minimally or non-responsive patients, not only because prospects for MCS patients are more favorable than for VS patients but also to ensure that consciousness in a non-responsive patient is detected (Healy, 2010). The results reveal that physicians are aware of weaknesses in the current diagnosis process and want a new diagnostic EEG-based tool. It must be highly valid, work reliably, allow for prognostic statements and not add to the burden of limited financial and personnel resources. The necessity of such an EEG-based tool to improve reliability of the diagnosis is widely acknowledged as current clinical assessment is influenced by individual skills of the physician.

To conclude, a practical, reliable and valid EEG-based diagnostic tool would be highly welcome in clinical and rehabilitative routines. Thus, the ERP-based paradigms to delineate the level of consciousness and cognitive function in otherwise non-responsive patients need to be validated such that only the most reliable and informative are applied when time is limited. The decision of which paradigm works best for which level of consciousness or cognition requires normative studies with representative healthy samples. The prognostic value of such paradigms can only be determined in longitudinal studies. A preliminary study with the BAC in a small sample of patients is described in the next section.

Tests on Patients with DOC and Locked-In Syndrome

The ERP paradigms proposed above were tested on a group of DOC and LIS patients. One reason to study LIS patients is to establish patterns of evoked potentials within BCI paradigms in brain

injured patients who do not exhibit disorders of consciousness but are behaviourally quite similar to non-responsive patients.

Methods

Here we describe and compare the results of 6 DOC patients in acute and chronic stages, recruited in the Post-Coma Unit of the Neuro-Rehabilitation Hospital “Fondazione Santa Lucia” in Rome, and of 9 chronic LIS patients (> 1 year in LIS, 6 female, 3 male, mean age 40 ± 9 years) from the French Association for Locked-in syndrome (ALIS) tested with MMN, and the passive and active P3 of the BAC developed within the DECODER project. Diagnosis of VS (n = 3) and MCS (n = 3) was based on the CRS-r. EEG was recorded with an active 32-electrode cap with two biosignal amplifiers g.USBamp (g.tec medical engineering GmbH, Austria) and recordings were processed and analysed with the NPXlab2012 software (www.braininterface.com). Data were pre-processed with Independent Component Analysis (ICA). Independent components corresponding to ocular artifacts were removed and other artifacts were removed by means of a threshold criterion (*i.e.* signal segments exceeding $70\mu\text{V}$ in absolute value). Components of interest were analyzed by visual inspection and by running a t-test. Differences were considered statistically significant for $p < 0.05$ if they appeared simultaneously at least on two electrodes and they lasted a minimum of 50 consecutive milliseconds.

Results

With regards to DOC patients, the Mismatch Negativity (MMN) was observed in three of six patients and the P300 was present in all but one patient in both the active and the passive conditions (Table 1). In one LIS patient, tests were stopped due to fatigue. Data from two patients (3 and 7) were discarded due to excessive artefacts. In the six remaining LIS patients, four presented

Table 1. Results from the 6 DOC and the 6 LIS patients analyzed. (+) = presence of ERP component;(-) = absence of clearly recognizable ERP components.

	MMN	P300 Passive	P300 Active
MCS 1	+	+	+
VS 2	+	+	+
MCS 3	-	+	-
MCS 4	-	+	+
VS 5	-	+	-
VS 6	+	-	+
LIS 1	-	-	+
LIS 2	-	-	+
LIS 4	-	+	+
LIS 6	-	+	+
LIS 8	-	+	-
LIS 9	-	-	-

an active P3; three a passive P3; and none had an MMN (Table 1).

Discussion

The auditory P300 and the MMN can offer a valuable supplement to early routine clinical examination and prediction of neurological outcome of post-comatose patients. From the data collected in this small patient sample, it seems that the presence of the considered components is not related to the severity of the disorder of consciousness, but rather to the different states of the brain, in terms of site and extent of the lesions. The MMN component points to a sufficiently spared pre-attentive sensory memory system (Näätänen et al., 2007), while the presence of the P3 suggests that working memory updating (Coles et al., 1988) is functioning in most of these patients.

Results in LIS patients revealed a response to the higher cognitive function paradigm (the active P300 task) even in the absence of the MMN and P300 in the passive condition. Regarding the MMN, a reduction of this ERP component has

been described in patients with cognitive deficits (Duncan et al., 2009). In LIS patients, a study has shown a moderate and selective cognitive impairment that is not related to the location of the lesion (Rousseaux et al., 2009). However, this does not explain the absence of an MMN in LIS patients. In this patient sample, the absence of lower level components (see Figure 3) and even the passive P300 did not indicate the absence of higher level components (active P300). This has important implications for the diagnosis of altered states of consciousness, confirming previous work (Kotchoubey et al., 2005) that this hierarchical approach is flawed.

The Hierarchical Approach in Clinical Assessment

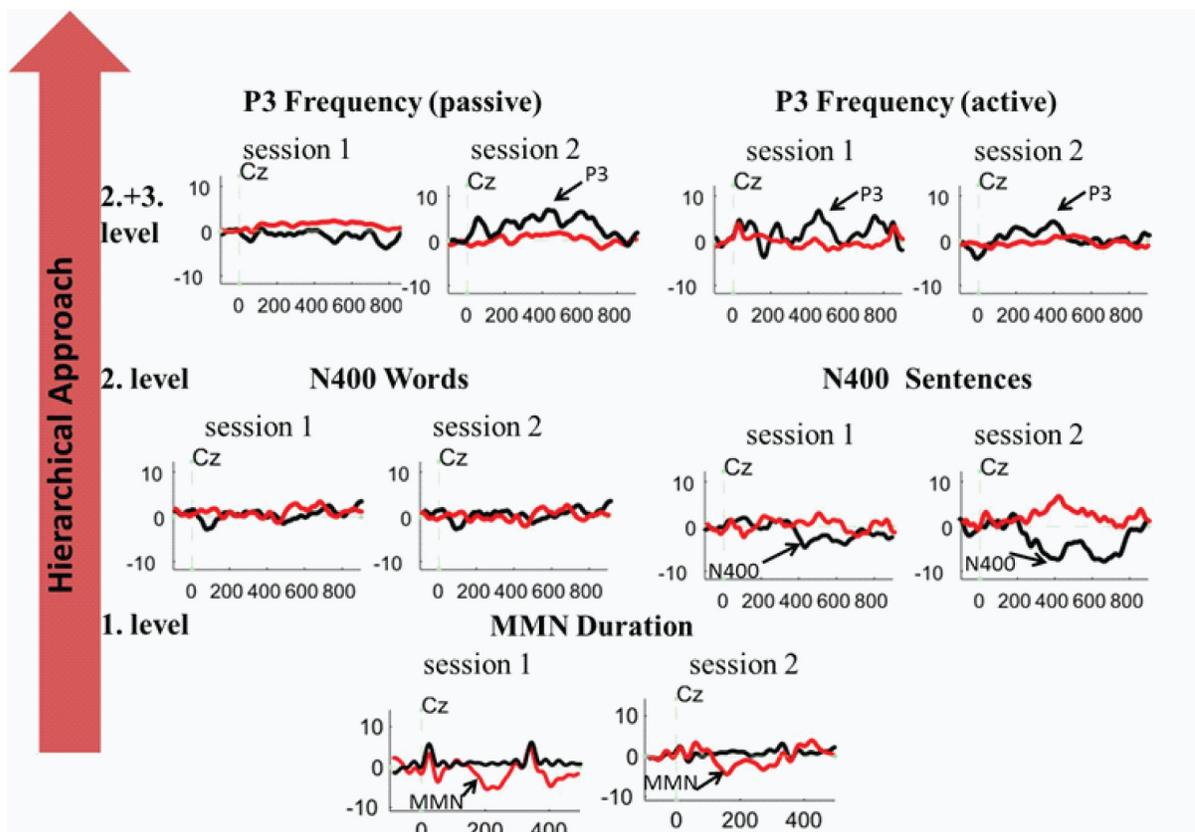
Another concern with the hierarchical approach involves its use within the daily clinical routine. For example, is it appropriate to stop assessing patients after one or two paradigms (corresponding to the first and second level) that do not yield promising ERP findings? Figure 4, like the preced-

ing section, indicates that stopping assessment so early is not justified by the data. This minimally consciousness state (MCS) patient (male, 35 years, coma onset 253/254 days) was examined twice using the same hierarchically ordered set of paradigms. The results revealed no correlation between both semantic paradigms (a positive ERP outcome in the word pair paradigm was not a prerequisite for the sentence understanding paradigm) and no correlation between the passive and active frequency oddball paradigms (a positive ERP outcome in the passive condition was not a prerequisite for the active condition). Thus, no informative conclusion about the present state of the patient could have been drawn if he were tested only with a single paradigm. However, a prerequisite of such an assessment is the patient's

ability to generally perceive sensory stimuli. Thus, further EEG analysis appears meaningless only if a frequent (standard) tone does not elicit even a primary cortical ERP complex P1-N1-P2. Otherwise, all passive paradigms and at least one active oddball or one more active paradigm (*e.g.*, dichotic listening, Yvert et al., 1998; a semantic oddball, Kotchoubey & Lang, 2001; or negated sentences, Herbert & Kübler, 2011) should be conducted in each patient before a final conclusion about the level of consciousness can be drawn.

In addition, this example shows that several measurements within one patient should be performed to increase the reliability of the assessment. Repeated measurements help to minimize error due to the well-known phenomenon of fluctuating arousal and attention in these patients. Further-

Figure 4. ERP responses of a VS patient. The black arrows point to significant components in which the two stimulus classes differ within an auditory paradigm – specifically, the P3, N400 and MMN.



more, the development of appropriate paradigms for low- or non-responsive patients requires a difficult tradeoff between the reliability of the signal and the capacities of the patient. The longer the experiment is, the better the signal-to-noise ratio and, thus, the higher the data quality. However, the attention span of the patients is very limited and they might be overchallenged by long sessions. This balancing act is difficult and small estimation errors could yield misleading, but consequential results. Moreover, differences in ERP responses of patients need to be judged on the single subject level, whereas the ERP responses elicited by the paradigms described above are typically analyzed on the group level.

Analyses on a Single Subject Level: Concerns and Solutions

Traditionally, the presence and absence of ERP components are analyzed with respect to measures such as latency, polarity, topography and sensitivity to experimental manipulations (Picton et al., 2000). However, nearly all ERP research involves healthy subjects. These measures may be too weak to detect whether the experimental manipulation had an adequate effect on the mean amplitudes of P3 components (shown in Figure 4), because ERPs in brain-injured patients may occur with prolonged latencies, and, depending on morphological changes in brain and skull structure, with altered topography and polarities (Duffy, Burchfiel, & Lombroso, 1979; Kotchoubey, 2005; Duncan et al., 2009). Thus, analysts might erroneously interpret any differences between amplitude curves (elicited by two different experimental conditions like standard and deviant) as indicators of different brain processes. Conventional methods such as t-tests between two conditions at each sample and electrode positions may lead to unacceptable alpha inflation. Hence, we describe three correction procedures for the single-subject analysis of EEG data.

1. *False discovery rate* (FDR) is a term for various procedures designed to control the expected number of false positive findings (Groppe et al., 2011). Compared to classical procedures, *e.g.* Bonferroni's procedure, which control the family wise error and can be very conservative with large numbers of comparisons, FDR procedures provide adaptive error control, depending on the number of significant results. However, this approach may be problematic when trying to identify small differences in the absence of other, large differences, which might happen when analyzing data in a priori defined time-windows. Thus, effects declared as significant using FDR procedures might be difficult to replicate when using a priori defined time windows (Groppe et al., 2011).
2. Another procedure was originally proposed by Guthrie & Buchwald (1991). This method takes into account that consecutive EEG samples – and any derived measures, such as t-values – are not independent, but show a high autocorrelation. By using an empirically derived estimation of this autocorrelation, it is possible to define a minimum length for the duration of series of values exceeding a predefined cutoff. In contrast to FDR, the effectiveness of Guthrie-Buchwald's procedure does not depend on the magnitude of observed effects, but on their duration. Thus, this method is most effective to detect long drawn out differences between two ERP curves, like the P3. Conversely, it is not suited for the detection of short differences, as the probability of short series might be judged to be too high, assuming a given autocorrelation. Further, Blair & Karniski (1993) have highlighted the problem of, among others, accurately estimating the autocorrelation of EEG data.
3. The *Studentized Continuous Wavelet Transform*, originally proposed by Bostanov & Kotchoubey (2006), analyzes EEG data

in the two-dimensional time-frequency domain. First, the continuous wavelet transform (Mallat, 2007) is calculated for each segment of EEG data. Second, a statistical map is created by calculating the t -values associated with the wavelet coefficients at each point in the time-frequency plane between two experimental conditions. Third, local extremes are detected in this statistical map. Finally, t -max randomization tests are used to determine which local extremes represent true vs. false differences in activation.

Each method has strengths and weaknesses. Thus, it is important to realize that effective diagnosis and analysis depends on both sensitivity and specificity. Any imbalance, such as high sensitivity but low specificity (when using multiple unadjusted comparisons) or low sensitivity but high specificity (when using FDR (Bonferroni) corrections) is likely to impede progress of the assessment (Real et al., 2013).

ERP Analyses of Single Trials: Concerns and Solutions

There is a growing interest in decoding ERP components at the level of single trials. This could be useful in many ways, such as identifying mental states or user's intentions so BCIs can be applied for medical purposes. However, this issue remains very challenging due to the extreme trial-to-trial variability. One way to deal with the problem of single-trial detection of relevant components of the EEG signals is the use of detection algorithms, also called classifiers. Classifiers are mathematical tools designed to accurately recognize a relevant feature from single trial data to ultimately estimate if the brain can distinguish between two or more external stimuli (*e.g.* deviant versus standard). Once the accuracy of such a discrimination process is computed, its statistical significance with respect to the chance level can be evaluated by

means of statistical tests (*e.g.* chi-square test). The significance of the accuracy strictly depends on the number of classified trials and is measured by means of a p -value. This procedure can provide an index about the reliability of the discriminated responses, and thus it could support clinicians in DOC patients' evaluation. Relevantly, such methodology is independent from the used protocol.

To better illustrate the potential advantage of such a procedure for medical applications of BCIs, like the detection of mental processing in absence of behavioral signs, we present results of its application on EEG data sets obtained from two patients diagnosed as VS. They were administered a classical acoustic oddball P300-based paradigm (2nd level of the hierarchical approach), during which they were asked to mentally count the deviant tones (targets, $T=60$) against the standard (no-targets, $NT=420$). Significance threshold was set at 5%. In one patient, the classifications (step-wise linear discriminant analysis - SWLDA) across 109 trials were random ($p>0.05$) for both target (49.06%) and no-target (60.71%) classes. In the second VS patient, the accuracy was 65.38% and 78.33% for target and no-target classes, respectively. Both classes were significantly classified ($p_{\text{target}}=0.027$, $p_{\text{no-target}}=0$).

It is mandatory to stress that the absence of a positive result, as in the first case, could be ascribed to many factors independent from the diagnosis of VS, thus preventing any definitive conclusions with regards to the clinical diagnosis. False negative inducing factors may be: vigilance status at the time of the recording (patient was sleeping); cognitive function masked by the DOC that affects the auditory task accomplishment; high signal to noise ratio; or the classifier was not effective enough to extract relevant features. One recommended solution is to conduct multiple recordings, as described above, at different times and/or to test different translation algorithms to identify the best appropriated for the relevant features. On the other hand, a possible occurrence of false

positives (statement on the presence/intactness of patient's cognitive processing ability) has to be considered. In this case, one source of errors might be the capture of brain response components not directly related to a voluntary shifting of attention between the two classes (target and no-target) that interfere with the algorithm classification output. A careful stimulation protocol design is the first step to prevent such an error source.

Overall, this section provides further support for the view that conventional DOC assessment procedures are inadequate, and that EEG-based measures can provide an effective, standard and easy methodology to detect residual cognitive activity in DOC patients. However, progress is hampered by procedural errors, which we discussed along with some solutions. The next section introduces the mandatory step for DOC patients provided consciousness was detected, *i.e.* a means of communication.

BCI: The Challenge and a Possible Solution

There are many challenges in developing a system that can detect consciousness, particularly with individual patients and single trials. However, if a non-responsive patient is consciously aware, then a new challenge arises: how can we establish communication in such a patient? A single-switch BCI (ssBCI) may be able to detect one specific brain pattern of a patient and use it to control different kinds of applications. Since each patient will react differently, the DECODER project explores several brain signals.

When designing a BCI for non-responsive patients, the specific cognitive characteristics of these patients have to be considered. Therefore, the BCI needs to be very simple and robust, meaning it should function even if only a single brain pattern can be reliably detected in that patient. Since individual patients will react differently, mental imagery (Horki et al., 2012; Müller-Putz et al., 2013), P300 (Müller-Putz et al., 2012;

Pokorny et al., 2013), and steady-state evoked potentials (Pokorny et al., 2011; Lesenfants et al., 2013) were explored. The P300 paradigm was implemented with auditory and vibrotactile stimulation. As examples, the methods for the auditory BCI and for the motor imagery based BCI will be described here.

Methods and Signal Processing

In the auditory P300 paradigm, two different tone streams composed of short beep tones with infrequently appearing deviant tones at random positions were used as stimuli (Müller-Putz et al., 2012; Pokorny et al., 2013). The streams were presented simultaneously with asynchronous onsets. By intentionally shifting attention from one stream to the other, the P300 response elicited by the deviant tones in the attended stream should be modulated. This paradigm was evaluated in ten healthy subjects and applied to twelve MCS patients (four female, eight male), aged between 14 and 66 years, at four different locations. EEG measurements were conducted in Graz (Albert Schweitzer Clinic), Würzburg (Intensive Care Hospital Schwaig), Rome (Fondazione Santa Lucia) and Liège (CHU University Hospital). This study was approved by the local Ethics Committees at all participating institutions and informed consent was obtained from the patients' legal representatives. A SWLDA classifier together with 10x10 cross-validation was used to infer which tone stream was attended. Moreover, all data segments from one participant were averaged according to stimulus type and target stream, and significant differences ($\alpha = 5\%$, length $L \geq 30$ ms) between (i) standard and deviant tones and (ii) target and non-target deviants were estimated by bootstrapping using 1000 bootstrap samples.

In the mental imagery paradigm, we explored whether complex mental imagery and attempted feet movement could be reliably detected in DOC patients (Horki et al., 2012; Müller-Putz et al., 2013). Four male patients in MCS aged

21 – 65 years participated in this study at Albert Schweitzer Clinic in Graz. Informed consent was obtained from the patients’ legal representatives. This study was approved by the Ethics Committee of the Medical University of Graz. The participants were instructed to perform the following tasks: sport - imagine performing one sport of your choice in the first person perspective; navigation - imagine navigating through your house, and looking around each room; feet - attempt (repeatedly) feet dorsiflexion. Fisher’s linear discriminant analysis (LDA) was used as a classifier based on logarithmic band power features calculated for multiple frequency bands (α : 8–13 Hz; β L: 13–19 Hz; β M: 19–25 Hz; β U: 25–30 Hz). A nested blockwise cross-validation (10x10 inner fold; leave-one-block-out outer fold) was applied to estimate the classification accuracy of each task versus reference.

Results

In the P300 paradigm (Müller-Putz et al., 2012; Pokorny et al., 2013), results for healthy subjects were promising, and most classification results were clearly better than random. However, single trial classification results were above chance level

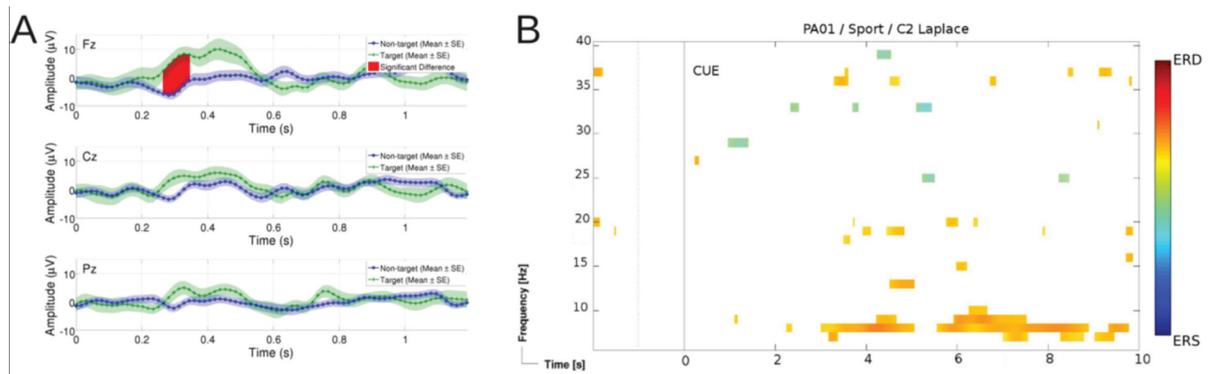
in only one of the twelve MCS patients. In four of the patients, the presence of a P300 could at least be detected on a single trial basis when presenting only one of the tone streams. However, none of the results were sufficient for communication purposes. Nevertheless, signs of consciousness were detected in most patients, not on a single trial basis, but after averaging of corresponding data segments and computing significant differences (Figure 5A).

In the mental imagery paradigm (Horki et al., 2012; Müller-Putz et al., 2013), one patient showed patterns of activation over sensorimotor area as during at least one task involving either simple (*i.e.* feet dorsiflexion) or complex (*i.e.* sport) motor imagery (Figure 5B) in each of the two sessions. Two other patients showed patterns of activation over central sensorimotor area for complex motor imagery task in the first session. In one of the four patients, no significant results were found.

Evaluating Protocol Performance with a BCI-Based Approach

A BCI-based methodology was implemented to evaluate the used protocols. This methodology is

Figure 5. Examples of brain patterns found in minimally conscious patients. The two panels show significant differences that reflect mental awareness. (A) Significant P300 at channel Fz using the auditory P300 paradigm. (B) Significant ERD differences at channel C2 (orthogonal Laplacian derivation) in the alpha band using the mental imagery paradigm.



standardized, as it is independent from the protocol itself, the extracted features, and the used classifier. It is based on the evaluation of classification performances stored into a confusion matrix (CM) (Bianchi et al., 2007), and also on the assessment of the statistical reliability of classification accuracy. Briefly, once the classification accuracy is computed, by considering the number of trials in each classification class (sport, navigation, feet, target, non target, etc.), it is possible to assess how much such accuracies differ from what a random classifier would return (Billinger et al., 2013; Yuan et al., 2013). This information is complementary to the data obtained from the study of brain patterns, as it allows researchers to understand the significance and reliability of a detected brain response. Furthermore, it could help to identify the best task to setup the ssBCI based on the residual skills of each patient.

Discussion

In the auditory P300 paradigm, single-trial classification results were not sufficient for communication purposes (Müller-Putz et al., 2012; Pokorný et al., 2013). Nevertheless, since significant deflections were found on an average level, this paradigm might still be useful to support clinical assessment of patients, and to provide them with a means of communication. In principle, since time is not a crucial factor for unresponsive patients, communication could be established by simply averaging data over many trials and detecting significant differences due to attention. To improve the paradigm, different stimuli (*e.g.*, words instead of tones) that may be easier to distinguish or elicit a stronger P300 response might be beneficial in the future (Ricci et al., 2013).

Using mental imagery, on the other hand, seems to be a more promising approach for some patients to communicate their intent (Horki et al., 2012; Müller-Putz et al., 2013). Classification

accuracies above chance were estimated for the feet and/or the sport mental imagery, but not for the navigation task. This is in line with previous findings indicating that, among other tasks, motor imagery rather than spatial navigation most frequently results in better classification performance (Friedrich et al., 2012).

Conclusion and Future Directions

Another method that may work well for detecting command following and testing communication in non-responsive patients is based on modulation of steady-state visually evoked potentials (SS-VEPs) using covert visual attention (Lesenfants et al., 2013). In future applications, one alternative approach to realize an ssBCI might involve attention-modulated steady-state somatosensory evoked potentials (SSSEPs). The feasibility of such an ssBCI was already shown in healthy subjects (Pokorný et al., 2011). The usage of a tactile P300 BCI system with patients is explained in more detail in the next section. To conclude, initial results presented here, as well as the results of other similar studies (Goldfine et al., 2011; Cruse et al., 2011), indicate that some DOC patients could communicate their intent using EEG.

COMMERCIAL SYSTEMS: MINDBEAGLE

Patients normally stay in a rehabilitation institution for several months before they are released to professional home-care, a home for handicapped people, or to a private home - often without professional or technical support. Hospitals typically have medical assessment and rehabilitation facilities in the same unit. In these institutions, it is advantageous to have a system that can assess the cognitive functions of the patients in frequent intervals to show trends and can allow patients

to communicate if cognitive functions are still present. Notwithstanding the described caveats, emerging EEG-based methods can facilitate both diagnosis and communication. The EEG is inexpensive, portable, widely available and objective, and has been used in hospitals for many years. However, practical EEG systems for non-expert users in home settings are not common.

As noted in the section titled “Requirements for an EEG-based diagnostic battery for patients with DOC”, interviews with experts indicated that the most important properties of an assessment and communication system are:

- Dependence on EEG only (due to problems with fMRI and other means);
- Fast and easy mounting of electrodes;
- Automatic data analysis and result presentation;
- Ease of use by medical / technical assistants;
- Support for a test battery to assess cognitive function;
- The capability to provide communication for the patient;
- Cost; and
- Prognostic value of results.

The key purpose of such an EEG system is to assess cognitive functions and establish an interface for communication. This was realized through (i) auditory evoked potentials (AEP), (ii) vibrotactile (VT) evoked potentials and (iii) motor imagery experimental protocols. Both the auditory and vibrotactile experiments are designed to elicit a P300 response similar to a P300 spelling device. A P300 spelling device is a BCI that presents different characters on the computer screen, which each flash individually or in certain patterns. The user is asked to concentrate on just one of these characters. Whenever this character flashes, a P300 component appears in the EEG data. After several repetitions, the signal-to-noise ratio increases to a level that the BCI can detect

and thereby select the corresponding character. This allows paralyzed patients to communicate (see Kaufmann et al., 2013c for the most recent result in patients with severe motor paralysis).

However, P300 BCIs based on visual stimuli do not work with patients who have lost their vision. Auditory paradigms can also be implemented using a frequent stimulus with a certain frequency and an infrequent stimulus with another frequency (see above). The user is asked to count how many times the infrequent stimulus occurs. Like with the visual P300 speller, the infrequent stimuli also produce a P300 response in the EEG. The same principle can be used for vibrotactile stimulation if *e.g.* the right hand is frequently stimulated and the left hand is infrequently stimulated. The EEG will also exhibit a P300 if the user is paying attention to the infrequent stimuli. This auditory and vibrotactile setup can assess whether the patient is able to follow instructions and in an experimental procedure (Kaufmann et al., 2013b). To answer yes and no questions, it is necessary to extend the vibrotactile setup to 3 stimulators. One of the stimulators applies the frequent stimuli, and 2 stimulators apply the infrequent stimuli. The user can concentrate on one of the infrequent stimulators to say (in this case) yes or no. Typically, an evoked potential is calculated by averaging the frequent and infrequent stimuli. A statistical analysis helps to visualize statistically significant differences, which is especially important for patient data collected in field settings, which is frequently noisy.

As noted above, motor imagery may also be used to control a BCI. In this case, the patient has to imagine a right or left hand movement for two-four seconds. This will result in an event-related desynchronization (ERD) and event-related synchronization (ERS) over the sensorimotor regions. Synchronization with the EEG data is necessary to avoid delays and jitters. The BCI system analyzes the acquired EEG data in real-time by implementing source derivation, pre-processing, parameter estimation and classification algorithms. Finally,

Figure 6. Left, top: mindBEAGLE system with EEG cap, active EEG electrodes, g.USBamp amplifier, vibrotactile stimulator, in-ear headphones and a laptop computer running the software. Left, bottom: vibrotactile stimulators on the left and right hand. Right, top: BCI accuracy trend over several days. Right, bottom: EP of electrode position Cz with statistical test between target and non-target auditory stimuli. The EP shows a significant P300 response. The bottom curve shows BCI accuracy over a number of target stimuli.



the BCI system decides whether the user imagined left or right hand movement, which can be used as a control signal to answer yes and no questions. If several repetitions are performed, the BCI system can calculate a mean accuracy that shows if the user is able to follow instructions. With two choices, such as yes or no, 50% accuracy would correspond to random classification.

The mindBEAGLE system (see Figure 6, left side) contains all these features and consists of an EEG amplifier with 16 channels that uses a 24 Bit analog to digital converter for high precision. The amplifier samples the EEG data at 256 Hz and sends the data via USB to the laptop computer system. Active EEG electrodes are used to get a robust EEG recording and avoid skin abrasion. They eliminate most of the artifacts from cable movements and power line interference. Therefore, high quality EEG recording can be performed

even in an unshielded room. Sixteen active electrodes can be mounted with conductive electrode gel, normally within about 2 minutes, including ground and reference electrodes. The reference is mounted on the left ear lobe and the ground electrode is located on the forehead.

The laptop controls the data acquisition, experimental paradigm, signal processing and result presentation. To provide auditory stimulation, the laptop also has an internal audio interface which can stimulate the left and right ear via in-ear headphones and sends a trigger signal to the signal processing module for synchronization. For the vibrotactile stimulation, the system uses stimulators like those shown in Figure 6, left side. In this case, one stimulator is mounted on each wrist, and switched on to stimulate the hand for several hundred milliseconds. Both are connected via USB to the computer and are controlled in

real-time through the experimental paradigm. For the motor imagery experiment, auditory instructions like “move the left hand” or “move the right hand” are given via the internal sound board. Perfect synchronization between the EEG data and auditory and tactile stimuli is critical to avoid delays or jitters.

The right side of Figure 6 shows the results for the auditory stimulation paradigm, using the evoked potential for electrode Cz on the vertex as an example. The Event-Related Potential (ERP) consists of the non-target averages (blue line) and of the target average (green line) from 100 ms before the stimulus onset until 700 ms post-stimulus. The green area around 250-350ms indicates the statistically significant P300 response for this electrode with $p < 0.02$. The accuracy plot reaches 100% accuracy after 5 target stimuli, which shows that the BCI system can perfectly discriminate the P300 response provided a sufficient number of trials. This resulting accuracy is also logged into a trend analysis to assess the patient’s P300 response over time.

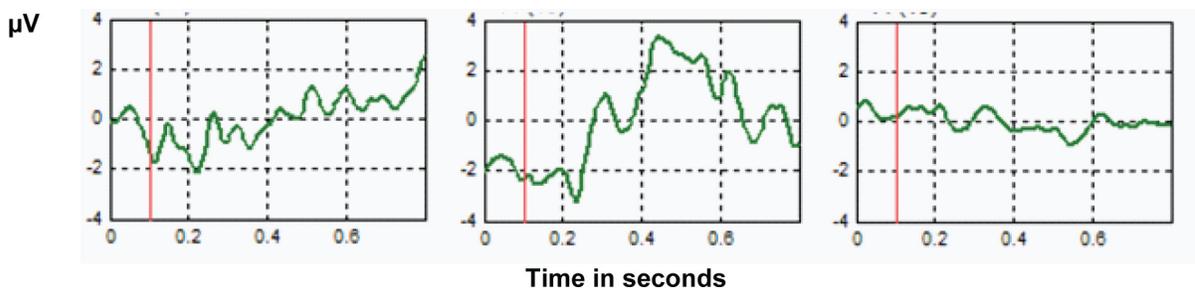
The results for the vibrotactile experiment with 2 stimulators are similar to the results from the auditory experiment. The ERP waveform and BCI accuracy can be used to interpret the results. To answer questions in the vibrotactile paradigm, the subject is equipped with stimulators on each hand and the neck. Each of the stimulators is switched on for 100 ms with a short break in between. The

subject is asked to focus on one of the stimulators and to count how many times it vibrates. Then, a caregiver asks a question and starts the paradigm. Like *intendiX* (www.intendix.com) or other visual P300 spellers, this elicits a P300 for the target stimulator, as shown in Figure 7, which allows the system to make a “yes” decision. Another kind of yes/no control approach was implemented with the motor imagery based BCI system, in which left or right movement imagery corresponded to “yes” or “no”.

In summary, *mindBEAGLE* can assess auditory and vibrotactile P300 and motor imagery responses, which can help identify whether the patient is able to follow instructions. If a P300 response is detected with the statistical ERP analysis or with the BCI algorithms, then it is very likely that the patient can understand instructions and concentrate on the task. The same is the case for the motor imagery paradigm. The trend analysis helps to identify fluctuations and helps to optimize treatment. Since many patients have impaired vision, the motor imagery, auditory and vibrotactile paradigms are better suited to their abilities, and can also produce reliable results. However, these results must be confirmed with more DOC patients.

After the initial assessment with a positive P300 response, the patient can also be trained to use the system for communication. Using the auditory experiment and 2 stimulators, the patient

Figure 7. Vibrotactile P300 communication via stimulators placed on the left hand, right hand and neck (left, middle, and right panels, respectively). The middle panel shows a clear P300 when the subject attends to the right hand stimulator.



can simply generate a click. With 3 stimulators and the motor imagery experiment, the patient can even answer yes and no questions, and thus the mindBEAGLE provides an ssBCI as described above that can be used with DOC patients.

Hence, mindBEAGLE is a new, practical EEG based system that can work even in noisy, real-world environments. This section and the previous section about single-switch BCIs showed that new, EEG-based solutions can address some of the problems inherent in conventional EEG-based tools for diagnosis and treatment. Next, we continue our discussion of challenges and potential solutions by considering a different tool to measure brain function in DOC patients.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS): ANOTHER EMERGING SOLUTION FOR COMMUNICATION IN DOC PATIENTS?

Background

Compared to the EEG or fMRI, fNIRS is a relatively new and rarely applied non-invasive functional brain imaging method. It measures a hemodynamic brain signal, similar to fMRI (Irani et al., 2007; Villringer & Chance, 1997), and also shows similar vascular sensitivity (Huppert et al., 2006). Like fMRI, fNIRS relies on the neurovascular coupling and, thus, only *indirectly* measures local brain activation through hemodynamic changes that accompany changes in neuronal activity. In terms of signal acquisition, however, fMRI and fNIRS methods differ considerably.

Functional NIRS is based on the penetrability of biological tissue by near-infrared light (composed of wavelength of 650-950 nm). Emitter optodes (*sources*) that are placed on the head send out light that passes through the skull and the brain. On its way through the brain, the chromophores

of oxygenated (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) within the blood vessels absorb the light according to their particular optical properties (Fallgatter et al., 2004; Irani et al., 2007). The remaining (reflected) light is picked up by detector optodes (*detectors*) placed on the head surface within a few centimeters from the sources. As oxy- and deoxy-Hb differ with respect to their absorption spectra (*i.e.*, they absorb light of particular wavelengths), one can then calculate the relative concentrations for both of them separately from the amount of light attenuation (the ratio of emitted to reflected light) by using a modified Beer-Lambert law (Cope & Delpy, 1988; Cope et al., 1988). Based on these concentrations, one can infer the functional state of neuronal tissue ('active' or 'non-active'). However, because of many uncontrollable influences, the absolute concentrations of the chromophores cannot be measured. Therefore, the exact brain activation level cannot be determined (Fallgatter et al., 2004). Nevertheless, relative changes in the signal time course are sufficient for localizing brain functions or for BCI applications, similar to fMRI.

Compared to fMRI, the main advantages of fNIRS are portability and reduced sensitivity to head movement artifacts. This makes fNIRS technology usable at the patients' bedside (for diagnostic purposes) or even beyond clinical settings in daily-life situations, *e.g.* for motor-independent communication. Moreover, fNIRS is relatively affordable, less technically demanding, and easier to operate. This might allow larger patient populations to benefit from hemodynamically based BCI applications. Furthermore, it does not require exposing patients to a strong magnetic field, and hence can be used close to paramagnetic medical equipment. Another advantage of fNIRS is that it is nearly silent. Thus, fNIRS can be regarded not only as a completely safe and harmless but also relatively comfortable method. While fNIRS has these benefits over fMRI, it only allows reliably measuring hemodynamic responses in cortical

tissue that is close to the head surface (up to approximately 3cm in depth). Thus, brain activation in, *e.g.*, subcortical structures cannot be measured that would be accessible with fMRI. Moreover, the spatial resolution of fNIRS (in the range of a few cubic centimeters) is considerably lower than the resolution obtained with fMRI (in the range of a few cubic millimeters).

While fNIRS has been applied in fundamental neuroscience since the early 1990s, it has only recently been recognized as a potential BCI measurement technology (Coyle et al., 2004; 2007; Naito et al., 2007; Sitaram, et al., 2007; Luu& Chau, 2009; Power et al., 2012). The following fNIRS study, performed in the context of the DECODER project, further explored the suitability of fNIRS for brain-computer interfacing.

Methods

Participants. Twelve healthy participants (age: 29.8 years \pm 9.6; five male, one left-handed) were included in the study that was approved by the local ethics committee of the Faculty of Psychology and Neuroscience at Maastricht University. All participants gave written informed consent.

General procedure, preparation and instruction. Seven mental tasks (*mental calculation, mental drawing, mental rotation, mental singing, mental talking, spatial navigation and tennis imagery*) were explained to the participants using standardized instructions. After ensuring that the participants understood each mental task, they were asked to choose the two mental tasks from the set that they thought are most easy and comfortable to perform. Participants had to undergo two identical functional runs. In each of these runs, they had to perform the two selected mental tasks nine times – three times for 5s, 10s, and 15s each. The two conditions alternated with resting phases of 20s in between. Participants were seated comfortably in a quiet room in front of a computer screen. They were instructed to engage in the mental task that was displayed on the screen

as immediately and continuously as possible, and to stop as soon as the resting instruction was indicated. During the resting phase, participants should not engage in a specific thought or task. Only the first three letters of the second part of the mental task's name were displayed on the screen (*e.g.*, “dra” instead of “mental drawing”) to avoid a visual stimulation that could automatically evoke task-specific brain activation (Nachev & Husain, 2007). For the same reason, the instructions were presented for only 2s followed by a fixation cross. Visual stimuli were presented using E-Prime 2.0 software (Schneider et al., 2002).

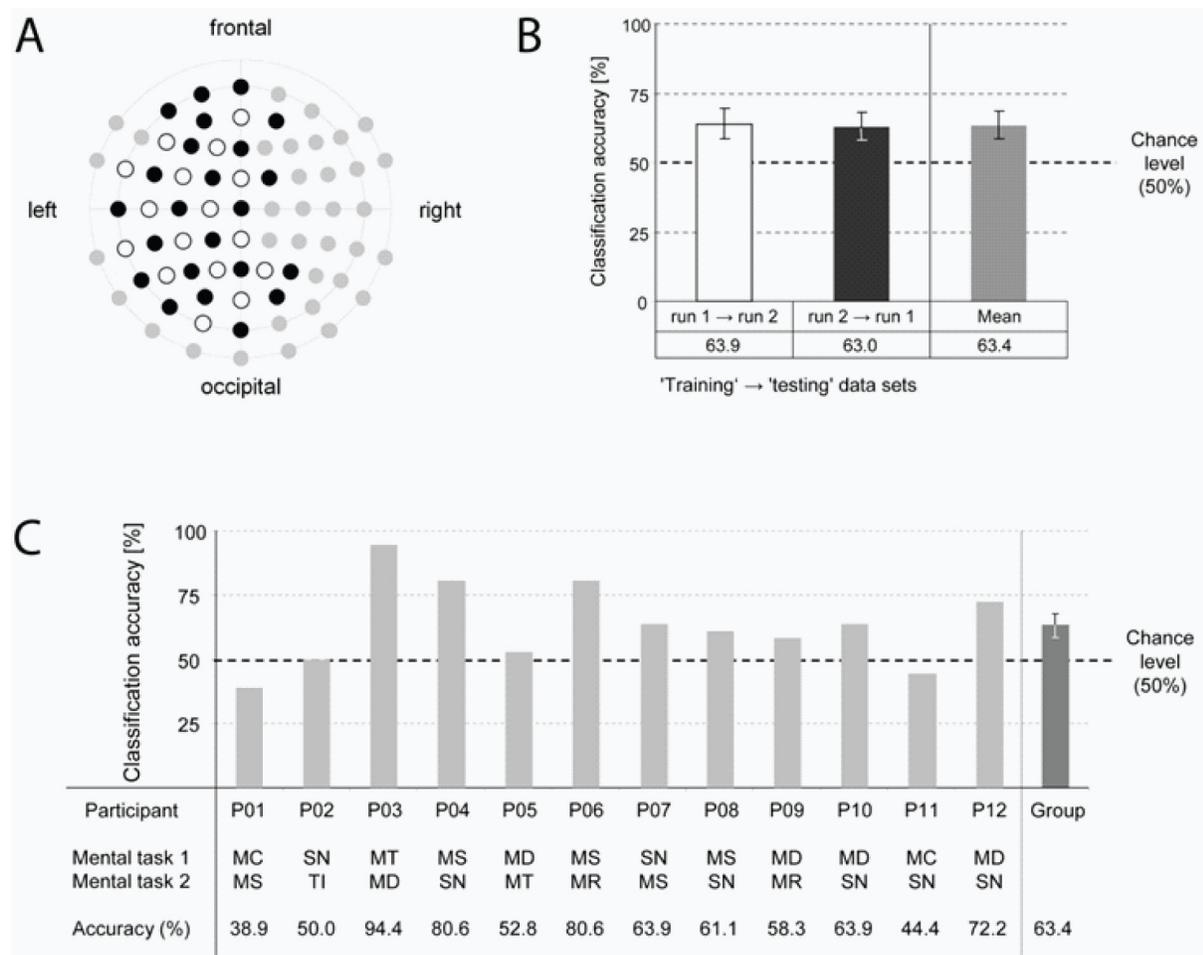
Data acquisition. fNIRS data were recorded with a NIRScout 816 upgraded to 16 sources and 24 detectors (NIRx Medizintechnik GmbH, Berlin, Germany). The data were recorded for 9 min 20 s for both 760nm and 850nm with a sampling rate of about 3.5 Hz. Because of the limited number of sources and detectors, a montage with high resolution was only feasible for a confined area of the scalp. The montage shown in Figure 8A was used in order to get high-resolution data for the left hemisphere.

Data analysis. fNIRS data were analyzed using *Satori* (v0.8, Brain Innovation B.V., Maastricht, The Netherlands). T-values for each channel for the oxy- and deoxy-Hb time courses were computed and used as features for a linear support vector machine (SVM). The first run's data were used to ‘train’ and the second run's data were used to ‘test’ the SVM classifier. The classification was repeated with the second run's data to ‘train’ and the first run's data to ‘test’ the classifier. For each participant, both of the obtained 2-task classification accuracies were averaged. Moreover, the mean 2-class classification accuracies obtained separately for the two different ‘training’/‘testing’ data sets were calculated.

Results

Each of the suggested mental tasks was chosen by at least one participant. *Spatial navigation* (n

Figure 8. Optode placement and classification results of the fNIRS experiment. Panel A shows a 2D representation of the optodes' montage. 40 optode locations were chosen to achieve a high-resolution coverage of the left hemisphere. White dots represent sources (16) and black dots represent detectors (24). Optrode positions are shown according to the extended 10-20 system of EEG electrode placement (Oostenveld & Praamstra, 2001). Panel B displays the mean classification accuracies obtained separately for the two different 'training'/'testing' data sets and their mean classification accuracy. Error bars indicate variance across participants (\pm standard error of mean – s.e.m.). Panel C shows the mental tasks selected and the achieved 2-task classification results for each participant. Moreover, the 2-task classification accuracy across all participants is displayed. Abbreviations/remarks: MC, mental calculation; MD, mental drawing; MR, mental rotation; MS, mental singing; MT, mental talking; SN, spatial navigation; TI, tennis imagery; error bars indicate variance across participants (\pm s.e.m.).



= 7) and *mental drawing* ($n = 5$) were generally preferred, whereas *tennis imagery* was selected by only one participant (Figure 8C).

Averaged across participants, the achieved 2-task classification accuracy was 63.4% (chance

level being 50% for differentiating between two mental tasks), which varied considerably between 38.9% (P01) and 94.4% (P03) (Figure 8C). The mean 2-task classification accuracies obtained

separately for the two different ‘training’/‘testing’ data sets only minimally differed (Figure 8B).

Discussion

In two thirds of the cases, the achieved individual 2-task classification accuracies were above 60%. However, it is critical to note that the obtained classification results varied considerably across participants. The high classification accuracy obtained for participant P03 indicates that, in principle, high classification performances can be achieved. Note that this participant was highly trained with regards to the mental tasks employed, whereas most other participants performed the mental tasks for the first time. This indicates that classification accuracies might considerably increase with intensive pre-training of the mental tasks, which might not be feasible when using fNIRS for assessing the level of consciousness, but should be possible in the context of motor-independent communication with BCI.

Future Directions

The aforementioned main limitations of fNIRS (relatively low spatial resolution, restricted depth pervasion) require a careful exploration of suited mental tasks that evoke differential brain activation patterns within superficial cortex regions (*i.e.*, in crowns of gyri). In this context, it might prove beneficial to exploit the high resolution of fMRI and to transfer gained information on the localization of brain function to the fNIRS technology. Thus, one idea would be to perform fMRI and fNIRS experiments in the same individuals – preferably simultaneously. In this context, the individual information gained from fMRI experiments could be further used to optimize (‘guide’) optode placement and therewith increase the

sensitivity of fNIRS. Additionally, more training data should be obtained, which will most likely increase classification accuracies. Moreover, fNIRS-based communication and control tools should be designed in a patient-tailored manner (e.g., individually selecting mental tasks) to optimize the separability of fNIRS brain activation patterns for each individual case and to make the device more comfortable. Finally, researchers should make a strong effort to explain the considerable inter-individual variability. The suggested combined fMRI and fNIRS measurements in the same individual may help in the future to better understand the observed inter-subject variability.

Taking into account the current state-of-the-art and the resulting opportunities for further development, we consider fNIRS-based brain-computer interfacing a promising technology with a clear potential for motor-independent communication.

CONCLUSION

Conventional methods for assessing the level of consciousness in patients with DOC and providing communication are insufficient. Both interviews with clinicians and numerous imaging studies have shown that misdiagnoses are common, even in hospital settings with well-established procedures. Furthermore, tools that can allow for communication are promising but require further development. Several advancements within the DECODER project and other efforts have further elucidated conventional problems and possible solutions, and have established foundations for improved portable systems that may rely on EEG and/or fNIRS. Different possible future directions were discussed within respective sections, supporting the overall conclusion that new, BCI-based technologies are advancing rapidly and are likely to

provide improved diagnosis and communication for patients with disorders of consciousness or in the locked-in state.

The issue of BCIs used in DOC patients may be regarded as key for further clinical practice, but there is relatively little work analyzing functional neuroimaging data in DOC patients. Our understanding of higher cognitive processes and related brain activity is too limited to develop thorough and precise methods to understand DOC patient data, and research such as in the DECODER project might help to change this situation. By developing BCI technology to assess, understand, and communicate with DOC patients, we might not only change the lives of these patients and their families and caregivers, but also solve some scientific, clinical and ethical problems. Thus, results and conclusions of the DECODER project provide a basis for improved guidelines and new clinical and research procedures. In the near future, BCI based systems for assessment and communication will become available that will allow us to use BCI technology with more patients and perform further scientific studies.

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KEY TERMS AND DEFINITIONS

Auditory Evoked Potential (AEP): A category of EEG activity elicited by auditory stimuli, such as tones or words. Other sensory information can produce other evoked potentials, such as visual evoked potentials (VEPs) or somatosensory evoked potentials (SEPs).

Battery for the Assessment of the Level of Consciousness (BAC): A series of tests that may be used to evaluate the patients' consciousness, which may result in a designation as minimally conscious or vegetative.

BCI (Brain-Computer Interface) or BMI (Brain-Machine Interface): A device that directly records activity from the central nervous system and translates it into messages or commands.

FES (Functional Electrical Stimulation): A device that artificially stimulates muscles, such as muscles responsible for grasping or hand movements. FES systems controlled by BCIs can restore some movement to people with spinal cord injury or other conditions.

Invasive: A category of BCI in which electrodes are surgically implanted on or in the brain.

Neuroscience: The study of the human nervous system.

Non-invasive: A category of BCI that does not rely on invasive sensors. Most non-invasive BCIs use electrodes placed in an electrode cap, which is worn on the head.

Robotics: A category of engineering focused on developing, building, testing, and improving robots.

Single Switch BCI (ssBCI): A type of BCI that provides control equivalent to one single switch, such as an ON-OFF switch for a light.

Vegetative State (VS): A condition in which users are unable to produce goal-oriented responses to stimuli, among other deficits.