CONVERGENCE OF FMRI AND EEG FOR DETECTION OF AWARENESS

MENTAL IMAGERY FOR THE DETECTION OF AWARENESS: EVALUATING THE CONVERGENCE OF FUNCTIONAL MAGNETIC RESONANCE IMAGING AND ELECTROENCEPHALOGRAPHIC ASSESSMENTS

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TITLE: Mental Imagery for the Detection of Awareness: Evaluating the Convergence of Functional Magnetic Resonance Imaging and Electroencephalographic Assessments.

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ABSTRACT

The accurate diagnosis of disorders of consciousness presents substantial difficulty because of the reliance on behaviour-based assessment tools. A patient may be covertly aware but unable to indicate their state due to physical impairments. Neuroimaging researchers have begun to seek alternate methods of assessment that rely on brain responses rather than behavioural ones. To this end, mental imagery has been employed as a voluntary cognitive activity that can be measured with fMRI or EEG to indicate awareness. In this dissertation I examine the advantages and limitations of these two imaging techniques and argue that EEG is more suitable for this patient population. I expand upon existing mental imagery research by exploring additional tasks that have not been applied to this problem, in order to address three previously unanswered questions that are central to the development of imagery-based diagnostic tools. First, do individuals differ on which imagery tasks produce the most reliable activation? Second, can the robustness of brain activation during imagery be predicted from familiarity with the imagined activity? Third, do fMRI and EEG provide converging evidence about individual imagery performance? In order to answer these questions, 6 mental imagery tasks were examined using simultaneous EEG and fMRI recordings, in combination with participant ratings. The findings revealed that, of the mental imagery tasks studied, mental arithmetic consistently produced the most robust activation at the single subject level. Additionally, there was no relationship between participants' familiarity with an activity and the level of brain activation during performance. The key finding demonstrated that EEG and fMRI were in agreement on

both of these questions, lending support to the increasing use of EEG over fMRI in disorders of consciousness.

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LIST OF ABBREVIATIONS AND SYMBOLS

3D	Three-dimensional
AAS	Average artifact subtraction
Ag/AgCl	Silver/silver chloride
ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
ASSET	Array special sensitivity encoding technique
BAEP	Brainstem auditory evoked potential
BCG	Ballistocardiogram
BCI	Brain computer interface
BOLD	Blood oxygen level dependent
BVA	BrainVision Analyzer
CRS-R	Coma Recovery Scale – Revised
CSF	Cerebrospinal fluid
DOC	Disorder(s) of consciousness
DMN	Default mode network
DRS	Disability Rating Scale
ECG	Electrocardiogram
EEG	Electroencephalography
EMCS	Emerged from minimally conscious state
EMG	Electromyogram
EPI	Echo planar imaging
ERP	Event-related potential

ERS/D	Event-related synchronization/desynchronization
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FSPGR	Fast spoiled gradient recalled
GA	Gradient artifact
GCS	Glasgow Coma Scale
GLM	General linear model
GLS	Glasgow-Liège Scale
GRE	Gradient recalled echo
HC	Healthy control
Hz	Hertz
ICA	Independent components analysis
IIR	Infinite impulse response
kHz	Kilohertz
kΩ	Kilo-Ohms
L1O	Leave one out
LIS	Locked-in syndrome
MCS	Minimally conscious state
MIQ-R	Mental Imagery Questionnaire - Revised
MLAEP	Middle latency auditory evoked potential
mm	Millimetre
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
mRMR	Minimal redundancy maximal relevance

ms	milliseconds
μV	Microvolts
OBS	Optimal basis set
PCA	Principal components analysis
PCC	Posterio cingulate cortex
PET	Positron emission tomography
PSD	Power spectral density
rbf	Radial basis function
RF	Radio frequency
ROI	Region of interest
SD	Standard deviation
SEP	Somatosensory evoked potential
SNR	Signal-to-noise ratio
SON	Subject's own name
SVM	Support vector machine
T	Tesla
TE	Echo time
TR	Repetition time
TTL	Transistor-transistor logic
UWS	Unresponsive wakefulness syndrome
VEP	Visual evoked potential
VMIQ-2	Vividness of Movement Imagery Questionnaire - 2
VS	Vegetative state

DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary author of the three articles included in this dissertation. I conducted the literature reviews and wrote the manuscripts, designed the studies, collected and analyzed all data. These studies comprised my doctoral research and are therefore included in the thesis. The roles of the co-authors for each paper and the dates the research was conducted are outlined below.

Harrison, A.H. & Connolly, J.F. (2013). Finding a way in: A review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness. *Neuroscience and Biobehavioral Reviews, 37,* 1403-1419.

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Guan, W. – stimulus programming, analysis consultation and programming, manuscript contributions

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PREFACE

This dissertation includes three original scholarly works: one review article and two empirical studies. The pages have been renumbered for continuity within this thesis but the notation and reference style of the journals have been retained. The review article provides an introduction to disorders of consciousness (DOC) and a thorough review of the use of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) for the detection of awareness and the assessment of cognitive function in this patient group – the main themes of the dissertation. As such, it will form the first, introductory chapter. The second article is a technical paper that deals with the correction of artifact in EEG data acquired simultaneously with fMRI. The learning of this technique formed a substantial and integral part of my doctoral research. This article elaborates on the methodology used in the core study, and adds to the discussion surrounding the choice of imaging modality for patients with disorders of consciousness. The third article is a normative empirical study of the agreement between fMRI and EEG measures of the effectiveness of various mental imagery paradigms for the elicitation of reliable, individual brain activation. This study provides evidence to guide the implementation of mental imagery paradigms using EEG and/or fMRI for the detection of awareness in patients with DOC, and a critical, but heretofore unverified, demonstration of the concordance between EEG and fMRI indices of mental imagery performance. The simultaneous EEG/fMRI recording and data processing methods, as well as the machine learning-based EEG analysis approach used in this study were technically advanced and the design, acquisition, data processing and analysis phases of this study required a substantial amount of time to complete. As a result, this single study contains the bulk of my doctoral research and therefore forms the core of the dissertation. The three articles are followed by a general discussion of the contributions, limitations, and future directions of the research presented herein.

CHAPTER 1: FINDING A WAY IN: A REVIEW AND PRACTICAL EVALUATION OF FMRI AND EEG FOR DETECTION AND ASSESSMENT IN DISORDERS OF CONSCIOUSNESS.

Harrison, A.H., & Connolly, J.F. (2013). *Neuroscience and Biobehavioral Reviews, 37*, 1403-1419. doi: 10.1016/j.neubiorev.2013.05.004.

Abstract

Diagnoses and assessments of cognitive function in disorders of consciousness (DOC) are notoriously prone to error due to their reliance on behavioural measures. As a result, researchers have turned to functional neuroimaging and electrophysiological techniques with the goal of developing more effective methods of detecting awareness and assessing cognition in these patients. This article reviews functional magnetic resonance imaging (fMRI) and electroenchphalography (EEG)-based studies of cognition and consciousness in DOC, including assessment of basic sensory, perceptual, language, and emotional processing; studies for detection of conscious awareness; paradigms for the establishment of communication in the absence of behaviour; and functional connectivity studies. The advantages and limitations of fMRI and EEG-based measures are examined as research and clinical tools in this population and an explanation offered for the rediscovery of the unique advantages of EEG in the study of DOC.

1. Introduction: Disorders of Consciousness, Diagnostic Difficulties, and the Importance of Accurate Assessment

Over the past few decades, improvements in emergency and intensive care medicine have resulted in an increasing number of patients who survive severe brain injury. While some patients recover well once they emerge from coma, others may remain in a vegetative or minimally conscious state. Together, coma, vegetative state (VS)[1], and minimally conscious state (MCS) are known as 'disorders of consciousness' (DOC). These are not to be confused with brain death, which is a complete and irreversible loss of all brain function (Medical Consultants on the Diagnosis of Death, 1981). Coma is a state of profound unresponsiveness in which the patient has their eyes closed and cannot be aroused with any amount of stimulation. Coma rarely lasts more than 10-30 days, after which time it is replaced by vegetative behaviour (Posner et al., 2007). The vegetative state (Jennett and Plum, 1972) is defined by a state of "wakefulness without awareness", meaning that patients have some form of sleep-wake cycling, but exhibit no evidence of awareness of self or the environment (Royal College of Physicians Working Group, 2003; The Multi-Society Task Force on PVS, 1994). Diagnosis is upgraded to minimally conscious state when a patient demonstrates inconsistent, but reproducible, evidence of purposeful behavior, usually in the form of command following (Giacino et al., 2002). Another diagnosis that is frequently included with DOC is locked-in syndrome (LIS). Patients with locked-in syndrome are conscious and have near-normal cognition, but are completely unable to move or speak (American

[1] Recently, the term "unresponsive wakefulness syndrome" has been proposed as an updated alternative name for vegetative state (Bruno et al. 2011; Gosseries et al. 2011; Laureys et al., 2010) We do not disagree with the adoption of an alternative to "vegetative state", which has unintentionally acquired a pejorative connotation, however, in this review we will use VS for the sake of consistency with the majority of the studies cited here, which were published before the term UWS was proposed.

Congress of Rehabilitation Medicine, 1995). LIS is often misdiagnosed as VS because, in its complete form, the behavioural presentation is exactly the same. The current taxonomy does not include LIS as a DOC, since consciousness is not impaired in LIS. However, the distinction between LIS and DOC is not always clear, since LIS can be a stage in recovery from DOC (Formisano et al., 2011). Locked-in syndrome presents a unique and fascinating set of issues for discussion, but the present paper focuses on diagnostic issues surrounding disorders of consciousness, specifically the vegetative and minimally conscious states. Table 1 contains a summary of the key diagnostic distinctions between DOC, brain death, and coma.

Diagnosis	Eye opening	Brainstem reflexes	Autonomic function	Behaviour	Communication	Cognition	Awareness
Brain death	Absent	Absent	Absent	None	None	None	No
Coma	Absent	Impaired	Impaired	None	None	Low-level	No
Vegetative state	Spontaneous or stimulus- induced	Preserved	Preserved	Non-purposeful	None	Low-level	No
Minimally conscious state	Present	Preserved	Preserved	Fluctuating but reproducible purposeful	Unreliable but intentional	Understand commands, environmentally contingent emotion	Partial
Locked-in syndrome	Present	Preserved	Preserved	Vertical eye gaze	Vertical eye gaze	Normal	Yes

Table 1. Diagnostic features of brain death, disorders of consciousness, and locked-in syndrome. Adapted from Giacino et al. (2009).

The fundamental distinction between VS and MCS lies in the assumptions about the underlying level of mental function in each case. A diagnosis of MCS implies that a patient has some level of conscious awareness – albeit fluctuating and inconsistent – but a diagnosis of VS carries with it the assumption that the patient is not conscious and therefore has no mental life. The definition of consciousness is a contentious, philosophical issue that has been debated for centuries. For our purposes, we make use of the ‘two-component’ definition widely accepted in medicine in which consciousness is composed of arousal (i.e., wakefulness) and of awareness (i.e., subjective experiences of self and environment) (Posner et al., 2007). Arousal is easily measured by the presence of eye opening, but awareness is fundamentally a subjective experience; therefore we can unequivocally establish that a person is conscious only if they can indicate, by some verbal or behavioural sign, that this is the case (see Connolly, 2012; Stins, 2009; Stins and Laureys, 2009). This becomes complicated when a person loses the ability to produce behavioural output, as in the case of DOC. A number of assessment scales exist for disorders of consciousness, some more precise than others (Seel et al., 2010), but all currently accepted methods have in common their reliance on bedside observations of behavioural signs of consciousness: a diagnosis of MCS depends on a patient’s ability to generate verbal or motor responses to commands, whereas a diagnosis of VS depends on the absence of such evidence (Royal College of Physicians Working Group, 1996). In this case, the absence of evidence is necessarily taken as evidence of absence – a logic that is fundamentally flawed. A person may be conscious but unable to produce any verbal or behavioural signals (e.g., Connolly et al. 1999; Owen et al. 2006), as is the case in complete locked-in syndrome and advanced neuromuscular diseases such as amyotrophic lateral sclerosis (ALS; Hayashi & Kato, 1989; Hayashi, et al., 1991). A patient with a DOC may have some conscious awareness, but be unable to respond due to sensory or perceptual impairments, aphasia, motor impairments, subclinical seizure activity, pain, fluctuating arousal, fatigue, and a range of other problems (Giacino et al. 2009). With conventional assessment tools such a patient would receive an inaccurate diagnosis of VS. This scenario is far from uncommon; in fact, misdiagnosis rates for VS are consistently estimated at about 40% (Andrews et al. 1996; Childs et al. 1993; Schnakers et al. 2009).

The importance of accurately making the diagnostic distinction between VS and MCS is thrown into sharp relief when one considers the many decisions about patient care that are made based on the diagnosis. MCS typically carries a better prognosis than VS (e.g., Giacino and Kalmar, 2005); long-term care support is funded partly on the basis of diagnosis, and referrals for rehabilitation are often not made if it is believed that the patient does not have the mental function necessary to benefit from it. Additionally, diagnosis has ethical and legal implications for end-of-life decisions concerning withdrawal of nutrition and hydration (Bressman and Reidler, 2010; Fins and Shapiro, 2007; Wilkinson et al., 2009), and pain management (Boly et al., 2008; Schnakers et al., 2010; 2012, Schnakers and Zasler, 2007). Not least of all is the potential emotional harm inflicted upon a covertly aware patient by careless bedside discussions of the patient's condition and prognosis.

New assessment tools that circumvent the reliance on behavioural output are necessary. A growing body of research seeks to address this issue by examining a patient's brain activity under various conditions, using functional neuroimaging and electrophysiological measures. These studies can be divided into three types, based on the experimental paradigms they employ: passive stimulation paradigms, active paradigms, and resting state or connectivity studies. In passive stimulation paradigms, subjects are presented with various stimuli and their brain responses are monitored for characteristic patterns indicative of normal cognitive processing. These paradigms do not require any intentional interaction—physical or mental—on the part of the patient. The question that inevitably arises from studies that employ passive paradigms in patients with DOC is whether the presence of typical patterns of activation to sensory and cognitive stimuli necessarily implies that they reflect conscious awareness. While normal brain responses to semantic ambiguity, for example, in a patient diagnosed as vegetative is an encouraging finding (Coleman et al. 2009), it is not sufficient evidence to conclude that a patient is consciously aware (Stins, 2009; Stins and Laureys, 2009). Many brain responses to stimuli are automatic, meaning that a person need not willfully process the information in order for a typical brain response to occur. For example, one cannot choose *not* to recognize a familiar face, or *not* to understand speech in one's native language. Indeed we know from studies of priming (Dehaene et al., 1998), sleep (Perrin et al., 1999; Portas et al., 2000) and anaesthesia (Davis et al., 2007) that some cognitive functions do occur in the absence of full conscious awareness. Therefore, in order to demonstrate that a patient is truly aware of self and environment, one must demonstrate *willful* modulation of brain activity; activation that would not appear unless the patient were intentionally performing the cognitive task in question. This is where active paradigms become relevant. Active paradigms involve some sort of instruction to the subject, either with or without accompanying stimulation. Brain responses are monitored for patterns of activation that could only occur if the subject has understood the instruction and has actively engaged in the mental task. Thus, mental imagery paradigms - for example imagination of physical activity or navigation - requiring the active involvement of participants have become a common method of tapping into consciousness in the absence of behaviour.

Very recently, a third avenue of investigation into neural correlates of consciousness has expanded rapidly, in part due to concerns over the high cognitive demands that active paradigms place on severely injured patients. In the same way as a patient may not be able to produce behavioural output as a result of their injury, a variety of factors may also prevent them from performing or sustaining the complex coordination of cognitive systems required to generate differential patterns of brain activity in an active paradigm such as a mental imagery task. Several groups have recently begun to use fMRI to investigate functional and effective connectivity between brain regions as a measure of consciousness, based on earlier positron emission tomographic (PET) findings that while 'islands' of cognitive function may be preserved, DOC are characterized by widespread functional network disconnection (Boly et al., 2004; Laureys et al., 1999; Laureys et al., 2000; Schiff et al., 2002).

In this article, we will review fMRI and EEG-based findings relating to the assessment of mental status in patients with disorders of consciousness, beginning with passive stimulation paradigms for the assessment of specific cognitive functions followed by active paradigms for the detection of awareness and the establishment of communication, and connectivity studies for the classification of DOCs. Note that we have included sample sizes for each study discussed for the information of the reader. A large majority of published studies in the field of DOC have very small sample sizes, and as a result cannot be generalized to larger patient populations. However, much can still be gained by examining small samples at the individual subject level. It quickly becomes apparent that current diagnostic criteria leave much to be desired. General patterns of performance emerge within diagnostic categories, but there are invariably exceptions – be it a VS patient who shows neuroimaging evidence of command following, or an MCS patient who can communicate at bedside but does not show corresponding neuroimaging markers of cognitive function. Thus, it is important to consider not only statistically powerful large group studies, but also individual patient results.

The literature review will be followed by a discussion of the relative advantages and limitations of fMRI and EEG as assessment tools in patients with DOC in the context of future research directions and the development of practical clinical tools.

2. Literature Review: Assessing Cognition and Consciousness with fMRI and EEG

The literature review in the following sections is summarized in Table 2.

2.1 Passive Stimulation Paradigms

Many cognitive functions are associated with reliable event-related potentials (ERP) and oscillatory patterns in EEG recordings, and with blood-oxygen level dependent (BOLD) activation patterns in fMRI studies. If these responses can be elicited in patients with DOC under the same conditions as in healthy controls, then inferences might be drawn reasonably about the cognitive functions that remain intact. The abundance of basic fMRI and EEG-based research on cognitive processes has enabled brain-injury researchers to select cognitive tasks that have robust activation patterns associated with them and adapt them for the purpose of assessing these specific processes in patients, from low-level sensory and perceptual processing, to emotion-modulated responses, to speech recognition and semantic comprehension. The following sections provide an overview of the use of fMRI and EEG-based measures in the assessment of cognitive functions in patients with disorders of consciousness.

Reference	Modality	Patient sample	Behavioral assessment	Task/Stimulus	Finding
Sensory/perceptual					
Cavinato et al. 2009	ERP	34 VS	DRS	SON oddball (SON deviant, sine tone standard)	P300 present in 23 VS
Cavinato et al. 2011	ERP	11 VS, 6 MCS	DRS	Auditory oddballs (sine tones, SON vs. tones, SON vs. other names)	P300 present in 6 VS and all MCS
Fischer et al. 2010	ERP	16 VS; 11 MCS	Repeated bedside exam	Duration deviant tones (MMN) and SON (P3)	MMN present in 2 VS and 3 MCS; P3 present in 3 VS and 4 MCS
Hinterberger et al. 2005	ERP	5 VS	Not reported	Auditory oddball (tones)	P300 absent in all patients
Holler et al. 2011	ERP	16 VS; 6 MCS	CRS-R	Complex tones with frequency deviants (MMN)	MMN present (delayed) in 2 VS; absent in MCS; present in only 11/15 HC
Kotchoubey et al. 2005	ERP	50 VS; 38 MCS	DRS	Auditory oddball and MMN with 3 levels of complexity	MMN present in 26 VS, 13 MCS; P3 present in 12 VS, 14 MCS;
Kotchoubey, 2005	ERP	50 VS	Not reported	Auditory oddballs (chords and vowel sounds)	P300 present in 13 VS for chords and 12 VS for vowels
Moritz et al. 2001	fMRI	1 VS	Not reported	Flashing light, speech, and hand touch, each vs. rest	Appropriate to all stimuli
Perrin et al. 2006	ERP	5 VS, 6 MCS, 4 LIS	GLS, CRS-R	SON oddball (SON deviant, other names standard)	P300 present in 3 VS, all MCS and LIS.
Qin et al. 2008	ERP	4 coma; 6 VS; 2 MCS	CRS-R	SON oddball (SON deviant, sine tone standard)	MMN present in 2 coma, 3 VS, 2 MCS
Rousseau et al. 2008	fMRI	4 VS; 5 HC	GCS, WHIM	Flashing light, tones, passive hand movement	1 VS - absent; 1 VS appropriate to all; 1 VS appropriate to tactile, absent to visual and auditory; 1 VS low activation to tactile and visual, absent to auditory
Speech/language					
Coleman et al. 2009	fMRI	22 VS, 19 MCS	CRS-R	Ambiguous sentences (with homophones/ homonyms)	Temporal activation to sound vs. silence only in 2 VS, 4 MCS; temporal activation to speech vs. noise in 7 VS, 12 MCS; temporal/frontal activation to semantic ambiguity in 2 VS, 2 MCS. Response absent in 13 VS, 3 MCS.
Connolly et al. 1999	ERP	1 MCS	Bedside exam	Sentences	N400 present
Fernández-Espejo et al. 2008	fMRI	3 VS, 4 MCS	DRS, Rancho Los Amigos	Narrative, reversed narrative	Temporal activation in 3 VS and 2 MCS to sound vs. silence, Temporal and inferior frontal activation to forward vs. reversed narrative in 1 VS and 1 MCS.
Hinterberger et al. 2005	ERP	5 VS	Not reported	Word pairs, sentences	N400 in 1 VS to sentences
Kotchoubey et al. 2005	ERP	50 VS; 38 MCS	DRS	Semantic oddball, word pairs, sentences	Semantic response present in 8 VS, 10 MCS
Kotchoubey, 2005	ERP	50 VS	Not reported	Word pairs, sentences	N400 present in 10 VS for word pairs and 9 VS for

					sentences
Schabus et al. 2011	ERS/D	10 VS, 4 MCS	CRS-R	Antonym pairs in sentences	No ERS/D in VS group, upper alpha ERS to unrelated word and ERD to antonym in MCS group, upper alpha ERD to unrelated and ERS to antonym in HC.
Schiff et al. 2005	fMRI	2 MCS	Repeated bedside exam	Narrative, reversed narrative	Temporal activation in both MCS similar to HCs for narrative vs. silence; reduced activation in MCS but not HCs for reversed narrative vs. silence.
Schoenle & Witzke 2004	ERP	43 VS, 23 MCS(-)	Not reported	Sentences	N400 present in 38% of VS, 77% of MCS
Familiarity/emotion					
Bekinschtein et al. 2004	fMRI	1 MCS	Bedside exam	Mother's voice and unfamiliar voice reading story	Appropriate auditory activation to unfamiliar voice vs. silence; amygdala, insula, and inferior frontal gyrus activation to mother's voice vs. unfamiliar voice.
Eickhoff et al. 2008	fMRI	1 coma	GCS	Light flicker, auditory words, tactile stimulation,familiar voices speaking SON or non-emotional words	Appropriate activation to visual, tactile, and word, with additional amygdala activation modulated by degree of familiarity of speaker and content.
Kothcoubey et al. 2009	ERP	15 VS, 12 MCS	Not reported	Emotional oddball (woeful exclamations vs. joyful)	Broadly distributed negativity ~150 ms in 4 VS, 2 MCS.
Laureys et al. 2004	ERP	1 MCS	WHIM, WNSSP, CRS-R	SON oddball (SON deviant, other names standard)	P300 to SON
Machado et al. 2008	EEG	1 VS	Not reported	Mother's voice vs. unknown female voice	Differences in gamma band for mother vs. silence; no difference for unknown women vs. silence.
Perrin et al. 2006	ERP	5 VS, 6 MCS, 4 LIS	GLS, CRS-R	SON oddball (SON deviant, other names standard)	P300 to SON in 3 VS, all MCS, all LIS
Qin et al. 2010	fMRI	7 VS, 4 MCS	CRS-R	SON spoken by familiar voice vs. silence	6 VS and all MCS showed activation in self-relatedness ROIs
Staffen et al. 2006	fMRI	1 VS	Not reported	Phrases containing SON or other name	Prefrontal activation to SON
Zhu et al. 2009	fMRI	9 MCS	Bedside exam	Familiar and unfamiliar photos	Greater volume of activation in visual networks to familiar photos than unfamiliar ones in MCS as a group.
Command following/awareness					
Owen et al. 2006	fMRI	1 VS	WHIM	Tennis and navigation imagery	SMA activation to tennis imagery and PHG, PPC, and PMC activation to navigation
Bekinschtein et al. 2009	ERP	4 VS, 4 MCS	CRS-R	MMN with local and global deviants, passive	3 VS, all MCS showed local MMN; 3 MCS showed global

				vs. counting	MMN in counting condition
Bekinschtein et al.2011	fMRI	5 VS	CRS-R	Hand movement command	Left premotor activation to right hand command in 2 VS
Cruse et al. 2011	ERS/D	16 VS	CRS-R	Right hand vs. toe imagery	Accurate machine learning classification of EEG in 3 VS.
Faugeras et al. 2012	ERP	24 VS, 28 MCS	CRS-R	MMN with local and global deviants, passive vs. counting	6 VS, 9 MCS showed local MMN; 2 VS, 4 MCS showed global MMN in counting condition
Goldfine et al. 2011	EEG	2 MCS, 1 LIS	Not reported	Swimming and navigation imagery	Consistent power spectral differences to imagery in LIS and 1 MCS.
Hinterberger et al. 2005	ERP	5 VS	Not reported	Hand motor imagery	LRP observed in 1 patient due to actual hand movement*
Monti et al. 2009	fMRI	1 MCS	CRS	Passive word listening vs. word counting	Activation of frontal, temporal, parietal and cerbellar regions similar to controls.
Monti et al. 2010	fMRI	23 VS, 31 MCS	Not reported	Tennis and navigation imagery	Appropriate activation in 4 VS and 1 MCS
Rodriguez-Moreno et al. 2010	fMRI	3 VS, 5 MCS, 1 EMCS, 1 LIS	CRS-R	Silent picture naming	LIS, EMCS, 2 MCS and 1 VS activated complete object-naming network in addition to visual cortex; 3 MCS and 1 VS activated partial network.
Schnakers et al. 2008	ERP	8 VS, 14 MCS	CRS-R	Passive SON vs. counting SON	Larger P300 to counted SON than passive SON in 9 MCS, 0 VS.
Schnakers et al. 2009	ERP	1 VS/TLIS	CRS-R	Passive SON vs. counting SON	Larger P300 to counted SON than passive SON
Communication					
Bardin et al. 2011	fMRI	5 MCS, 1 LIS	CRS-R	Swimming/tennis imagery vs. rest as command following and binary and multiple-choice communication	LIS, 2 MCS showed command-following; 1 MCS showed activation in multiple choice, but none in binary choice task.
Lulé et al. 2013	ERP	3 VS, 13 MCS, 2 LIS	CRS-R	4-choice auditory oddball	Command following in 1 MCS, 1 LIS; communication in 1 LIS only
Monti et al. 2010	fMRI	1 VS	Not reported	Autobiographical questions with tennis/navigation imagery for yes/no response	5/6 answers correctly determined
Resting state/functional connectivity					
Boly et al. 2009	fMRI	1 VS, 1 BD	CRS-R, SMART, WHIM, WNSSP, GLS	Resting-state BOLD	Reduced default-mode connectivity and absent cortico-thalamic connectivity in VS; absent connectivity in BD
Boly et al. 2011	EEG	8 VS, 13 MCS	CRS-R	Roving oddball MMN with dynamic causal modeling	MMN present in VS and MCS, but top-down connections present only in MCS.
Cauda et al. 2009	fMRI	3 VS	DRS	Resting-state BOLD	Reduced right hemisphere

					DMN connectivity, increased left hemisphere DMN connectivity in VS patients.
Fingelkurts et al. 2012	EEG	14 VS, 7 MCS	Bedside assessment, LCF	Resting state microstates	VS and MCS has fewer microstates; fast alpha microstates were correlated to diagnosis; delta, theta, slow alpha were negatively correlated to diagnosis.
Lehembre et al. 2012	EEG	10 VS, 18 MCS	CRS-R	Resting-state power spectra, and coherence	Increased delta and decreased alpha power in VS compared to MCS; lower connectivity in alpha and theta in VS vs. MCS.
León-Carrión et al. 2012	EEG	7 MCS, 9 SND	Coma/Near Coma Scale, Rancho Los Amigos, FIM+FAM	Resting state coherence	Reduced connectivity in MCS vs. SND, particularly of frontal regions from other regions.
Ovadia-Caro et al. 2012	fMRI	1 BD, 1 coma, 2 VS, 2 MCS, 1 LIS	CRS-R	Resting-state BOLD	Reduced interhemispheric connectivity in task-positive network, correlated with clinical level of consciousness
Soddu et al. 2011	fMRI	8 VS, 1 MCS, 2 LIS	CRS-R, GLS	Resting-state BOLD	Reduced DMN connectivity in VS and MCS patients, near-normal DMN connectivity in LIS patients.
Vanhaudenhuyse et al. 2010	fMRI	5 coma, 4 VS, 4 MCS, 1 LIS	CRS-R, GLS	Resting-state BOLD	Negative correlation between clinical level of consciousness and DMN connectivity

Table 2: Literature review summary.

Abbreviations: CRS-R = Coma Recovery Scale – Revised; DMN = default mode network; DRS = Disability Rating Scale; EMCS = emerged from minimally conscious state; ERS/D = event related synchronization/desynchronization; FIM+FAM = Functional Independence Measure + Functional Assessment Measure; GCS = Glasgow Coma Scale; GLS = Glasgow-Liège Scale; HC = healthy control; LIS = locked-in syndrome; MCS = minimally conscious state; MMN = mismatch negativity; SMART = Sensory Modality Assessment and Rehabilitation Technique; SND = severe neurocognitive disorder; SON = subject's own name; TLIS = total locked-in syndrome; VS = vegetative state; WHIM = Wessex Head Injury Matrix; WNSSP = Western NeuroSensory Stimulation Profile

* motor response to command suggests that this patient was incorrectly diagnosed as VS

2.1.1 Sensory, Perceptual and Pre-Attentive Processing

Many functional neuroimaging studies in vegetative and minimally conscious patients have focused on basic sensory and perceptual processing. These studies do not, in and of themselves, allow inferences to be made about a patient's level of awareness or cognitive ability, but they are crucial in the interpretation of findings from tasks that require higher-order cognitive processing, particularly negative findings. For example, in order to assess whether a patient can discriminate speech sounds from other auditory signals, we must first establish that the auditory cortex is intact functionally and shows activation to sound. Establishing this level of functioning provides some reassurance that a lack of activation to speech sounds is not simply due to a damaged auditory system that is equally unresponsive to all acoustic stimuli. Likewise, there is little to be gained by searching for responses to images of familiar faces without establishing that there is a functioning visual system. The pivotal role of establishing the integrity of a key element of the communication system is central to any assessment of cognitive function in the circumstances being discussed (see Connolly, 2012). Establishing the integrity of sensory systems with EEG is a well-established practice and has been performed as a routine part of brain injury assessments for decades (Chiappa, 1997). Evoked potentials are short-latency, time-locked EEG responses to sensory stimuli. Brainstem auditory evoked potentials (BAEPs) and middle-latency auditory evoked potentials (MLAEPs) are elicited by the presentation of auditory stimuli, and reflect the integrity of the auditory pathways and primary auditory cortex, respectively. Somatosensory evoked potentials (SEP) are elicited by electrical stimulation of the median nerve, and reflect integrity of the ascending somatosensory tracts and primary somatosensory cortex.

Visual evoked potentials (VEP) are usually elicited by a rapidly reversing checkerboard or grating pattern and reflect the integrity of visual input pathways and primary visual cortex (Schomer and Lopes da Silva, 2010).

One of the first studies to apply fMRI to DOC investigated BOLD responses to basic auditory, visual, and tactile stimulation in a single vegetative patient (Moritz et al., 2001). The patient demonstrated activation in the superior temporal gyrus bilaterally, as well as in the angular gyrus and middle and inferior frontal gyri of the left hemisphere in response to narrated text versus rest; in the posterior occipital pole bilaterally in response to flashing light versus rest; and in the central sulcus bilaterally in response to tactile stimulation of both hands – all responses that are typical in healthy subjects. However, this was a single case study, and evidence from subsequent studies shows that "normal" activation in patients with DOC is certainly not typical of this group. Rousseau et al. (2008) used a similar tri-modal stimulation paradigm in 4 VS patients with variable results. One patient showed no observable activation to any of the stimuli; another showed extensive activation in expected locations to all stimuli; a third patient showed appropriate activation to tactile stimulation but not to auditory or visual stimuli; and, the fourth showed very slight activation to tactile and visual stimuli but not to auditory. This study illustrates the importance of multi-sensory paradigms in neuroimaging assessments of patients with DOC – a patient may show no response in one modality, but given a different type of stimulation may show normal responses (e.g., Connolly et al., 2000). However, most studies in this area are still conducted primarily in the auditory modality, for a number of reasons. Firstly, auditory stimuli are by their very nature relatively impossible for a patient/participant to avoid. Patients in VS and MCS frequently have difficulty maintaining eye-opening and fixation for visual stimulation (e.g., Zhu et al., 2009); and tactile stimuli are generally more complex to deliver. Secondly, the integrity of the various components of the auditory system is easily established outside of the scanner using auditory evoked potentials. Absent or abnormal auditory evoked potentials can be used as exclusion criteria for auditory fMRI studies (e.g., Bekinschtein et al., 2011). Visual evoked potentials can also be measured in a similar fashion, but are less straightforward to interpret and can tell us very little about a patient's visual acuity over and above the basic function of visual pathways (Evans and Boggs, 2010). And finally, perhaps the most intuitive reason that functional neuroimaging studies of DOC focus on auditory stimuli is that speech is our primary method of communication and most fundamental form of interaction.

While auditory stimuli have advantages over other modalities in principle, using them in combination with fMRI presents several difficulties (see section 3.2.1) that limit the practicality of using fMRI in patients with DOC. ERPs do not suffer from these same limitations, making EEG a much more practical methodology for this purpose. The auditory 'oddball' is a very common paradigm widely used to investigate basic auditory discrimination and pre-attentive orienting responses. In its most basic form, a series of standard tones are presented, with the occasional deviant tone, which may differ from the standard tones in pitch, intensity, or duration. The deviant tone elicits a negativity at fronto-central electrode sites around 150-250 ms post stimulus called the mismatch negativity (MMN) (Näätänen et al., 2007). The MMN reflects pre-attentive auditory discrimination processes.

The same type of stimulus sequence can elicit an entirely different response called the P300 if the subject is actively attending to the stimulus (Polich, 2010). However, the P300 has proved particularly interesting in response to more complex stimulus environments than the simple oddball paradigm. One P300 variant (referred to as the P3a) is related to novelty detection and orienting behavior while another variant (the P3b) is widely regarded as a measure of memory function and active information processing. The P3a shows a more frontal topography and a more restricted temporal nature occurring between about 250-350 ms. In contrast, the P3b exhibits a parietal distribution and varies in time (typically between about 250-500 ms) depending on stimulus complexity. For example, one paradigm that will figure prominently in the discussion below involves the presentation (typically aurally) of lists of names (e.g., John, James, Amy) within which is also presented the subject's name (unsurprisingly known as the Subject's Own Name, SON, paradigm). The subject's own name enhances the P300 amplitude compared to other names and delays its latency compared to less complex stimuli (e.g., deviant tones in an oddball sequence) (Holeckova et al., 2008).

The MMN can be elicited in both VS and MCS patients, with a frequency ranging from about 13-50% with no significant difference in occurrence between patient groups (Fischer et al., 2010; Holler et al., 2011; Kotchoubey et al., 2005; Qin et al., 2008). Kotchoubey, (2003) demonstrated that the MMN is elicited more frequently and with greater amplitude by complex tones than by simple sine tones in patients with DOC – an important finding given that the MMN is one of the most useful components in predicting outcome in DOC (Daltrozzo et al., 2007; Fischer et al., 2000; 2010). Several studies have also investigated the P300 as an indicator of pre-attentional orienting and working memory updating on DOC patients, with equally variable results. Hinterberger et al. (2005) did not observe a P300 response to deviant tones in any of their 5 VS patients, while Cavinato et al. (2009) observed a P300 to the SON vs. tones in 68% of their VS sample (N = 34). Perrin et al. (2006) observed a P300 response in all members of a sample of LIS (N = 4) and MCS (N = 6) patients and in 60% of VS patients (N = 5). Other studies lie in between these two extremes: Kotchoubey and colleagues consistently report a P300 in about 30% of their VS and MCS patients (Kotchoubey, 2005, 50 VS patients; Kotchoubey et al., 2005, 50 VS patients and 38 MCS patients), with no differences between the two groups (Kotchoubey et al., 2005); Cavinato et al. (2011) observed P3 in all of their 6 MCS patients, and 6/11 VS patients. The variability in these results is attributable to many of the same factors as variability in fMRI results among patients with DOC, such as aetiology, diagnostic criteria, level of arousal – but also to the type of stimuli used to elicit the P3. Studies that used different levels of stimulus complexity to elicit the P3 (e.g., 3-component chords, vowel sounds (Kotchoubey et al., 2005), or SON (Cavinato et al., 2011)) found greater P300 responses, both in number and in amplitude, to the complex stimuli than to sine tones.

2.1.2 Speech and Language Processing

One of the most common questions regarding patients with DOC is "Can they understand us?" The majority of ERP and fMRI studies in these patients seek to answer just that question, not only in individual cases but also at the level of diagnostic category. The clinical diagnosis of MCS implies some level of speech comprehension indicated by reproducible responses to command, whereas the diagnosis of VS is based on the absence of such evidence. Many fMRI and EEG studies of DOC have investigated whether neuroimaging markers of language processing support these assumptions.

FMRI studies of spoken language function in VS and MCS patients typically focus on two main processes: speech recognition and semantic comprehension. The speech recognition paradigms have typically used narratives and signal-correlated noise or narratives played in reverse along with stimulus free periods to determine whether a patient is processing speech as speech or merely as general auditory input. Schiff et al. (2005) were the first to publish findings using this type of paradigm in patients with DOC. The study reports fMRI results from 2 MCS cases and 7 healthy controls who listened to narratives of familiar events read by familiar voices, or heard those same narratives played in reverse. In the forward narrative condition, both patients showed activation patterns similar to controls in the superior and middle temporal gyri. Interestingly, in the reversed narrative condition, controls showed similar patterns of activation as to the forward narrative condition; results interpreted as indicating that they recognized the narrative as speech, but simply meaningless speech. However, both patients showed severely reduced activation in this condition reflecting reduced processing of linguistically meaningless stimuli. While the results of the patients differ from those of the control group for the reverse-narrative condition, the results are still suggestive that the patients are processing speech signal as distinct from acoustically identical non-linguistic sound. Fernández-Espejo et al. (2008) used a similar paradigm in a group of 3 VS and 3 MCS patients compared to 19 healthy controls, and subsequently in another single VS patient (Fernández-Espejo et al., 2010). The results suggested that there is not a clear distinction between VS and MCS patients in terms of fMRI markers of speech recognition. When both narrative conditions (forward and backward combined) were contrasted with a silent baseline 3 VS and 2 MCS patients showed activation in superior temporal regions comparable to controls, reflecting intact auditory processing of complex sound. Of these 5 patients, 1 MCS and 1 VS patient also showed appropriate temporal and inferior frontal activation in the forward narrative condition compared to the backward narrative condition, reflecting language-specific processing. The remaining 1 MCS and 1 VS patient showed no significant activation in either contrast.

The studies reported above demonstrate that some patients with diagnoses of VS or MCS process speech as distinct from other auditory signals. However, these studies provide no indication of whether the speech stimuli are processed at a semantic level. A long history of ERP studies has provided a widely used and reliable marker of semantic processing, well-suited to this purpose. The N400 component is observed in response to a word that is incongruent with its semantic context and is indisputably linked to processes related to semantic comprehension (Kutas and Federmeier, 2011).

Connolly et al. (1999) were the first to employ the N400 to investigate semantic processing in a patient with a DOC[2]. They used a series of simple sentences whose terminal word was either congruent (e.g., "Father carved the turkey with a *knife*.") or incongruent (e.g., "The winter was harsh this *allowance*.") with the context of the sentence. Sentences were presented aurally and visually, in separate sessions. The patient's auditory N400 response demonstrated intact semantic processing, while the visual N400 did not, consistent with the patient's injury-related deficits. Kotchoubey and colleagues (Kotchoubey, 2005; Kotchoubey et al., 2005) used two different N400 paradigms to assess semantic processing in large samples of DOC patients: word pairs that were semantically related or unrelated, and sentences similar to those used by Connolly et al. (1999). Both studies observed evidence of semantic differentiation in the form of the N400 in approximately 25% of the 100 total VS and 38 MCS patients studied, with no significant differences between the groups in terms of the frequency of

[2] Strictly speaking, Witzke and Schoenle (1996) were the first do so, however their identification of the presence/absence of the N400 component was questionable. Additionally, the findings were published in German. Since this review was restricted to English-language articles, we cite Connolly et al. (1999) as the first.

an observed N400. Shoenle and Witzke (2004) observed higher rates of N400 response to semantically incongruent sentences – about 38% of VS patients (N = 43) and 77% of their “near VS” patient group (N = 23, who would fall in the MCS(-) category according to the Aspen Workgroup criteria). The differences in occurrence of the N400 between studies are attributable, at least in part, to the use of different criteria for identifying the component, illustrating the need for guidelines in quantifying ERPs in patient populations (Duncan et al., 2010). Schabus et al. (2011) took a different approach by examining oscillatory responses to semantic incongruity. They calculated event-related synchronization/desynchronizations (ERS/D) to antonym sentences (e.g., “The opposite of black is white/yellow/nice.”) in 10 VS patients and 4 MCS. They did not report individual-level results, but observed significant group-level differences in ERS/D between VS, MCS and healthy controls: VS patients showed no significant ERS/D, while MCS patients show an ERS to unrelated words and an ERD to antonyms in the upper alpha band, compared to the opposite response in controls (ERD to unrelated words and ERS to antonyms). The authors attribute this reversal to a difference in processing strategy in MCS patients vs. controls, wherein MCS patients do not anticipate the terminal word as controls do, but rather perform semantic integration in a post-hoc, bottom up manner.

A slightly different paradigm has been used to investigate semantic processing with fMRI. Semantically ambiguous sentences containing words that have homonyms (same spelling, different meaning) or homophones (same pronunciation, different spelling and meaning) are compared to unambiguous sentences which contain no such words. In a large group study (which included patients reported separately in Owen et al. 2005; 2006; and Coleman et al. 2007), Coleman and colleagues (2009) investigated semantic comprehension in a total of 22 VS and 19 MCS patients. 2 VS and 2 MCS patients showed some evidence of semantic processing in the form of temporal and/or frontal activation in the same areas as controls in response to semantically ambiguous vs. unambiguous sentences. 7 VS and 12 MCS showed temporal lobe responses to speech versus noise; 2 VS and 4 MCS patients showed activation to sounds vs. silence only; and 13 VS and 3 MCS showed no significant activation to any of the conditions, although some showed activation in appropriate areas below the threshold for statistical significance.

2.1.3 Familiarity and Emotion

An area of particular interest and importance for both clinician and families of DOC patients is emotion and sense of familiarity. Families of patients with DOC are frequently concerned about whether their loved one recognizes their voices, faces, or names. Familiar or emotional stimuli are especially salient and can evoke stronger responses than similar stimuli lacking the elements of familiarity or emotion (Holeckova et al., 2008). For this reason, such stimuli are well-suited to ERP and fMRI assessments, although few studies have employed them. Two common strategies to elicit responses related to familiarity are to compare responses to the subject's own name (SON) compared to other names (see section 2.1.1); and responses to familiar voices (usually the mother's) compared to unfamiliar voices. Laureys et al. (2004) report a single MCS patient who showed a P300 to his own name compared to other names. This finding was replicated by Perrin et al. (2006) in 3 out of 5 VS patients, all 6 MCS patients, 4 LIS patients, and 5 healthy controls. Machado et al. (2008) observed oscillatory changes in the gamma band in a boy in VS when he listened to his mother's voice, but not when the same words were spoken by unfamiliar women. In the only substantial group study of emotion in DOC, Kotchoubey et al. (2009) examined patients' ERP responses to woeful exclamations as oddball stimuli in a series of joyful stimuli (single words in which only the prosody determined the emotion). They observed a broadly distributed negativity occurring at around 150 ms in response to the emotional oddball in all healthy controls, and in 6 of the 27 VS and MCS patients studied. Staffen et al. (2006) reported a single VS patient who showed selective BOLD activation in the medial prefrontal cortex (similar to controls) to his own first name compared to other first names. Qin et al. (2010) observed BOLD activation in regions of interest related to self-reference processing (based on a more complex manipulation of degree of self-relatedness of name stimuli in 17 healthy controls) in response to the subject's own name spoken by a familiar voice in 6 of 7 VS patients and all 4 MCS patients. However, caution must be used in interpreting these findings. Although analyses were carried out in regions established in healthy controls to be relevant to self-referential processing, they did not employ an adequate control condition in the patient experiment: the self-referential stimuli were contrasted to a resting baseline only, and not to an equally complex, but non-self-referential stimulus. In an fMRI investigation of a rare long-term comatose patient (eyes remained closed at 35 months post-injury), Eickhoff et al. (2008) reported a particularly surprising finding. Not only did the patient show robust and appropriate activation to tactile and visual stimulation (with eyes taped open) but she also showed appropriate primary and associative auditory activation and left inferior frontal gyrus (Broca's area) activation to spoken words. Moreover, when the speech was directed to the subject by name, additional activation was observed in the left amygdala and right anterior superior temporal sulcus, and this activation was modulated by the familiarity of the speaker, i.e., the patient's children evoked the strongest response, followed by friends, with significantly weaker responses to unknown voices. In a related finding, Bekinschtein et al. (2004) reported an MCS patient who showed appropriate auditory activation when listening to a story read by an unfamiliar voice, but showed additional activation in the amygdala and insula when the story was read by the patient's mother. Although, as mentioned above, studies in the visual domain are rare in patients with disorders of consciousness, Zhu et al. (2009) have reported increased activation of visual association areas in MCS patients in response to historically familiar photos compared to unfamiliar ones.

2.2 Active Paradigms

2.2.1 Detection of Awareness

While demonstrations of intact perceptual, language, and emotional processing are essential to a complete assessment of a patient's cognitive status, they give us little insight into the patient's level of conscious awareness. We cannot know, without some form of report from the individual, whether they have any conscious experience of the stimuli they are processing. In order to conclude, in the absence of behaviour, that an individual is consciously aware, we must observe patterns of brain activity that could only occur if this were the case. Take for example the case reported in 2006, and since widely publicized, by Owen and colleagues of a young woman who had been diagnosed as being in a vegetative state (although the patient may have been exhibiting visual fixation indicative of transition to MCS (Posner et al., 2007, Chapter 9; Schnakers et al., 2008)). The authors employed an active mental imagery paradigm developed by Boly et al. (2007). While undergoing fMRI scanning, the patient was instructed to perform two mental imagery tasks: to imagine playing tennis, and to imagine navigating from room to room around her home. These tasks had previously been shown to elicit different and robust patterns of activation in healthy volunteers, particularly in the supplementary motor area for tennis imagery and in the parahippocampal gyrus, posterior parietal cortex, and lateral premotor cortex for navigation imagery (Boly et al., 2007). The patient's activation patterns were virtually indistinguishable from those of controls. This finding confirmed that she was able to understand the instructions given to her, and to respond to them by willfully performing the mental imagery task in the absence of any external stimulation, which in turn produced a typical pattern of fMRI activation, despite her inability to respond behaviourally. The authors therefore concluded that the patient was in fact consciously aware (see Greenberg, 2007; Nachev and Husain, 2007; Owen et al., 2007; Stins, 2009; Stins and Laureys, 2009 for further discussion of this case).

Though rare, the patient described by Owen et al. (2006) is not a one-of-a-kind case; the results have since been replicated. In the largest fMRI study of patients with DOC published to date (Monti et al., 2010), 23 VS and 31 MCS patients underwent fMRI scanning while being instructed to imagine playing tennis or navigating a familiar environment. Of this sample, 5 patients (4 VS patients and 1 MCS patient) were identified whose brain activity indicated that they were successfully performing the mental imagery tasks. Goldfine et al. (2011) used a similar task while recording EEG from 5 healthy controls, 1 LIS patient, and 2 MCS patients. They compared power spectra during imagery of swimming or navigation to resting baseline. The LIS patient and 1 MCS patient showed evidence of motor imagery task performance, as measured by the consistency of each patient's signal pattern changes across runs, rather than in comparison to healthy subjects' patterns. Similarly, Owen and colleagues (Cruse et al., 2011) observed command-following in the form of appropriate event-related synchronizations/desynchronizations (ERS/D) to motor imagery instructions in 3 out of 16 VS patients. The motor imagery task they employed, which the authors claim to have developed as 'novel', involves imagination of hand and foot movement and has in fact been used for over two decades in both basic research and in clinical research involving brain-computer interfaces in patients with motor and neuromuscular disorders (Kalcher et al., 1996; McFarland et al., 1997; McFarland et al., 2000; Müller-Putz et al., 2005; Neuper et al., 2003; Penny et al., 2000; Pfurtscheller and Neuper, 1997; Pfurtscheller et al., 1993; Pfurtscheller et al., 1997; Pfurtsheller, et al., 2000; Scherer et al., 2004; Wolpaw et al., 1991; for reviews see e.g., Neuper and Pfurtscheller, 1999; Neuper et al., 2006a,b; Wolpaw et al., 2002). Recently, a debate has arisen over the statistical methods employed by Cruse et al. in a re-analysis of the study's data by Goldfine et al. (2013) which suggests that Cruse et al.'s methods violate statistical assumptions and are biased towards falsely identifying awareness in VS patients. However Cruse et al.'s (2013) rebuttal argues that Goldfine and colleagues' methods are unsuitable for the data and equally error-prone in the opposite direction, making detection of awareness unlikely not only in patients, but also in a majority of healthy controls. They also point out that even with Goldfine et al.'s stringent statistical criteria two of the three patients in whom they detected awareness were pushed only slightly below accepted statistical thresholds, while the third remained significant. It is clear that the application of this technique for the detection of awareness is still in its infancy, and much further study is needed before its reliability as a clinical tool can be established. A cautious and critical eye must be employed when evaluating findings, and an attitude of open data sharing and scientific debate such as that demonstrated by Cruse and Goldfine and their colleagues will be essential to the development of a useful and reliable method of detecting awareness in patients with DOC.

The cognitive control required to generate statistically significant brain activation to complex mental imagery tasks is considerable. It must be noted that a subset of patients may be consciously aware, but unable to perform those specific tasks, for any number of reasons including impaired attention, fluctuating arousal, fatigue, selective damage to networks involved, misunderstood instructions, and so on. Other studies have attempted to compensate for some of these potential difficulties by using tasks that are somewhat less cognitively demanding, but still require willful processing on the part of the patient. Schnakers et al. (2008) developed an active ERP paradigm based on the commonly used "subject's own name" (SON) paradigm (e.g., Perrin et al., 2006) with the modification that subjects were asked to count the instances of their own name. The SON in the active (counting) condition elicits a larger P300 than in the passive condition in healthy subjects. Schnakers et al. (2008) observed P300 responses similar to controls in 9 out of 14 MCS patients. Conversely, none of the 8 VS patients showed a P300 in either the passive or active conditions. The same group detected a case of total locked-in syndrome using the same paradigm in a patient who would have been behaviourally diagnosed as comatose (Schnakers et al., 2009). Following suit, Monti, Coleman, and Owen (2009) reported a single MCS patient who was asked to listen to a series of words passively, or to listen to the same series of words and count the occurrences of a target word while undergoing fMRI. In 20 healthy controls, the target-counting task, compared to the passive listening task, elicited activation in a widespread network involving frontal, temporal, parietal, and cerebellar regions. The MCS patient showed activation of the same network to an extent that fell within the range of normal subject variability, suggesting that the patient successfully performed the target-counting task.

Bekinschtein et al. (2009) developed a novel ERP task based on the classic mismatch negativity (MMN) to detect awareness. A series of tones were presented which included both local deviants (every fifth tone) and global deviants (every fifth group of five tones had the same or different structure than the preceding four). In healthy subjects, the local deviant elicited an MMN and a P3a, and the global deviant elicited an additional but later P3b. However, the global effect was only observed when the participants were actively counting the global deviants and disappeared when they were mind-wandering or engaged in a visual interference task. The authors concluded that the global ERP effect required conscious awareness of the stimuli, and this was upheld by participant reports. The paradigm was subsequently tested on a group of 4 VS and 4 MCS patients. Three of the VS patients showed the local effect, but none of them showed the global effect. In contrast, all MCS patients showed the local effect and 3 out of 4 showed the global effect. This finding was extended in 2 further publications, the second encompassing the findings of the first: Faugeras et al. (2012) tested the same paradigm on 100 patients (including those reported in Faugeras et al., 2011), some of which were tested on several occasions. Sixty-five datasets were retained from 49 patients, the rest being excluded due to excessive artifact. Of these 49 patients, 24 were in VS, 28 in MCS, and 13 were conscious. The global effect was observed in all of the 8 healthy controls that were included in the analysis, in 54% of the conscious patients, 14% of the MCS patients, and in 8% of the VS patients. These patient results illustrate both the utility of ERPs for detecting conscious processing in DOC patients, and also the caution that must be used in interpreting negative results, since only half of the patients who were clinically assessed as conscious showed the ERP results indicative of consciousness in this paradigm.

Bekinschtein et al. (2011) used motor preparatory BOLD activity as a marker of purposeful behaviour in a sample of 5 VS patients who showed intact auditory evoked potentials and word-related fMRI activation, out of an original sample of 24 VS patients. Subjects simply received instructions to move their left or right hand. Only the control subjects were able to actually move their hands, but two of the 5 VS patients showed movement preparatory activity in the left premotor cortex to the right hand command. None showed activation to the left hand command, possibly due to lesions selectively affecting the right hemisphere.

Only one study has investigated volitional cognition in the visual domain. Rodriguez-Moreno et al. (2010) used a picture-naming task to probe consciousness in 5 MCS, 3 VS, 1 patient who had emerged from MCS (EMCS) and 1 LIS patient. Subjects were asked to silently name drawings of objects as they were presented. Control subjects activated a language-related network, outside of the visual network, known to be selectively activated by picture naming versus passive viewing. The locked-in, EMCS, 2 MCS and 1 VS patient activated the complete network, 3 MCS patients and 1 VS activated a partial network, and 1 VS patient did not show activation in the naming network.

The results of the studies reviewed so far illustrate the incongruity between clinical diagnoses and neuroimaging assessments of cognitive function. Some patients with a diagnosis of vegetative state showed evidence of high-level cognition and even awareness; whereas some diagnosed MCS patients – who showed behavioural evidence of purposeful behaviour and therefore some level of conscious awareness – failed to show activation even at the level of primary auditory cortex (Coleman et al., 2009). The implication for vegetative patients is clear: some patients who have received a diagnosis of vegetative state may actually be misdiagnosed cases of MCS, or even locked-in syndrome. However, negative findings in MCS patients are somewhat more puzzling, but could be attributed to damage to auditory pathways (in cases where subjects have not been pre-screened with auditory evoked potentials), to fluctuating levels of arousal, to cortical responses too weak or variable to reach statistical significance, or to alterations in neurovascular coupling (see section 3.3.1). Add to this already complex issue the diagnostic disagreements between different behavioural assessment methods and there is little wonder that fMRI and EEG findings appear to be at odds with diagnosis on occasion, again underscoring the need for comprehensive, multimodal, hierarchical assessments to gather evidence about a patient's true mental status.

2.2.2 Communication

Once it has been established that a patient who has been diagnosed as vegetative is indeed conscious despite outward appearances, the question becomes "What can be done for this patient?" Aside from intensifying rehabilitation efforts, all attempts must be made to establish some form of communication. When the patient does not have the physical capacity to make behavioural responses, we must again turn to their brain responses. A vast literature exists on the use of electrophysiological measures as means of communication with and control of devices (known as brain-computer interfaces, BCI) in physically disabled populations (see e.g., Birbaumer et al., 2006; Curran and

Stokes, 2003; Daly and Wolpaw, 2008; Neuper et al., 2006; Nicolas-Alonso et al., 2012; Wolpaw et al., 2002). These systems make use of various EEG signals, including slow cortical potentials (e.g., Birbaumer et al., 2000), the 'oddball' P300 ERP (e.g., Donchin et al., 2000), and sensorimotor ERS/D (e.g., Pfurtscheller et al., 1993; Wolpaw et al., 1991), which are translated into various outputs like cursor movement, spelling, or prosthesis control. These devices have been developed primarily for application in ALS, but the potential application to DOC is obvious (Chatelle et al., 2012; Kübler & Kotchoubey, 2007; Kübler, 2009; Naci et al., 2012). This vast body of existing knowledge on EEG-based BCI had not been applied in DOC until very recently, and it had rarely been cited in the DOC literature, even when the techniques developed by BCI researchers were being employed directly, as in Cruse et al. (2011). Until very recently, the field has overwhelmingly remained focused on fMRI as the technique of choice for detecting awareness and establishing communication in patients with DOC.

Using the same strategy as many BCIs, Monti et al. (2010) explored the use of mental imagery conditions in fMRI for basic communication (e.g., yes/no questions) in patients with disorders of consciousness. From the 5 patients who showed modulation of BOLD activation in the mental imagery tasks discussed in section 2.2.1 above, 1 VS patient with reliable responses was chosen to undergo the communication experiment. The patient was posed a series of autobiographical questions and asked to respond by using one of the imagery conditions (i.e., playing tennis or navigating) for "yes" and the other for "no". In 16 healthy control subjects, a blinded experimenter was able to determine the answers to the questions based on activation patterns in individual subjects with 100% accuracy. In the patient the answers to 5 out of 6 questions were correctly determined based on the mental imagery responses (the 6^{th} question showed virtually no activation in the regions of interest for either imagery condition).

Bardin et al. (2011) used a modified version of the Monti et al. (2010) paradigm to attempt simple communication with 5 MCS patients and 1 patient with locked-in syndrome. They simplified the imagery task slightly by using only one imagery condition (physical activity imagery, expanded to other activities like swimming) and a rest condition in place of the second imagery task. They first investigated whether the expected activations could be reliably elicited to command. Appropriate activation to the imagery task was observed in all 14 healthy controls, 2 MCS patients and the locked-in patient, with no activation observed in the other 3 MCS patients. Control subjects and 4 patients then underwent 2 communication scans: a binary choice and a multiple choice. In the binary choice task, subjects were asked a yes/no question and asked to perform the physical activity imagery for “yes” and do nothing for “no”. In the multiple-choice task, subjects were shown a face card from a deck of playing cards and asked to remember it. During the scan the four possible suits and four possible faces were presented verbally and subjects were asked to respond using the imagery task when they heard the options that corresponded to their cards. In both the binary and multiple-choice conditions, blinded experimenters were able to determine the healthy volunteers’ answers with 100% accuracy. However, only one patient (MCS) showed observable activation in the multiple choice condition, with no successful data in the binary condition, a result which is especially puzzling because 2 of the 3 patients who failed to produce BOLD responses were in fact able to communicate at the bedside. This result speaks directly to the preliminary nature of these methods and the need for much more research before this technique can be considered a reliable clinical tool. It also reiterates the degree of caution required in interpreting negative BOLD findings (see section 3.3.1 below).

Lulé et al. (2013) attempted to apply an auditory oddball EEG-based BCI paradigm to probe command following and establish communication in 2 LIS, 13 MCS, and 3 VS patients. One LIS patient was able to demonstrate command following and use the BCI for communication. One MCS showed some evidence of command following, but none of the MCS or VS patients were able to use the BCI for communication. EEG-based BCIs hold obvious potential for patients with DOC but clearly much work has yet to be done to optimize both the input and the classification algorithms for this population.

2.3 Resting State Activity and Functional Connectivity

Research into resting state activity and connectivity is arguably the fastest growing area in the field of neuroimaging in DOC. Part of the rationale for these studies is that the types of paradigms used in the studies reviewed above require at a minimum intact sensory pathways, and at a maximum highly coordinated cognitive function, and that these methods should be complemented by tools that do not depend on sensory integrity or a patient's ability to understand instructions. Earlier PET studies provided evidence that islands of cognition may remain intact in patients with DOC, and that reduced cortico-cortical and thalamocortical connectivity may lie at the heart of impaired consciousness (see Schiff and Laureys, 2012 for discussion and an eloquent model of consciousness as an emergent property of frontoparietal connectivity). As a result, more and more studies are investigating the nature of resting-state activity and connectivity using both fMRI and EEG.

The default mode network (DMN, Raichle et al., 2001) has been a particular area of focus for fMRI connectivity studies in DOC. The DMN encompasses the posterior cingulate cortex/precuneus, medial prefrontal cortex, and temporoparietal junctions and is particularly intriguing because it is more active at rest than during an attention-demanding task (Raichle et al. 2001). Recent research in DOC suggests that an intact default mode network may be a prerequisite for consciousness, and may therefore serve as a potentially useful marker in diagnosis. Boly et al. (2009) found reduced functional connectivity in the DMN of a vegetative patient compared to 6 healthy controls; and absent DMN functional connectivity in a brain dead patient. Cauda et al. (2009) also found impaired default mode networks in 3 VS patients, and observed a qualitative correspondence between a behavioural measure of function and DMN impairment. Vanhaudenhuyse et al. (2010) studied DMN connectivity in 4 VS, 4 MCS, 1 locked-in, and 5 coma patients and observed an exponential correlation between DMN connectivity and clinical level of consciousness that was particularly pronounced in the precuneus/PCC region. Similarly, Soddu et al. (2011) observed fewer connections in their 8 VS patients than in controls; but connectivity comparable to controls in their 2 locked-in patients. Ovadia-Caro et al. (2012) investigated interhemispheric functional connectivity between homologous regions, not in the DMN, but rather in the opposing, "extrinsic" task-positive network. They observed reduced connectivity in DOC patients compared with controls, and also a correlation between the clinical level of consciousness and the degree of interhemispheric connectivity. Several very recent studies have also investigated connectivity using EEG power spectra, with similar findings. Lehembre et al. (2012) analyzed power spectra in 10 VS and 18 MCS patients, and observed increased delta power and decreased alpha power in the VS group compared to the MCS group. They also observed lower connectivity in the alpha and theta bands in the VS group than in the MCS group. León-Carrión et al. (2012) found stronger connectivity between anterior and posterior brain regions in a group of 9 patients with severe neurocognitive disorders compared to a group of 7 MCS patients, who showed a disconnection particularly between frontal cortex and other brain regions. Fingelkurts et al., (2012) studied EEG microstates in 14 VS and 7 MCS patients compared to 5 healthy volunteers and observed that the DOC patients had fewer microstates than healthy controls. They also found that microstates characterized by fast alpha oscillations were positively related to the clinical level of consciousness, whereas microstates characterized by delta, theta, or slow alpha oscillations were negatively related to clinical level of consciousness.

Resting state functional connectivity appears to have a relationship to level of consciousness, and holds the advantage of not relying on potentially damaged sensory, perceptual, and cognitive systems. However, even more insight could be gained by studying functional connectivity under task conditions. To our knowledge, only two studies have investigated functional connectivity under cognitive stimulation. Boly et al. (2011) employed dynamic causal modeling to ERP responses during an MMN task to examine not only functional connectivity but also effective connectivity, that is, directional, causal connections between brain regions. They found that while VS patients were still able to generate an MMN response, they lacked a top-down connection from frontal to superior temporal cortex. This connection was preserved in MCS patients, who did not differ significantly from controls. This finding lends further support to the notion that isolated cognitive processes may be preserved in VS, but that deficient connectivity is at the heart of decreased consciousness. Kotchoubey et al.

(2013) studied global functional connectivity under emotional load in 6 VS and 6 MCS patients who listened to recorded human pain cries compared to non-emotional vocalizations. While they observed no significant stimulus-related activation in either group in a typical GLM analysis, a whole brain functional connectivity analysis revealed stronger connectivity in the MCS than in VS patients, in emotion-related networks similar to those observed in healthy controls.

The studies in this section support a link between functional connectivity and consciousness; however caution must be used when interpreting these findings at the individual subject level, as they are based on a tautology. The problem lies in the fact that these studies have used behavioural measures as the independent variable 'level of consciousness'. While the level of functional connectivity appears to be related to the patient's *behaviour*, we know from the body of research discussed in earlier sections of this review that behavioural measures are not always reliable indicators of conscious awareness. Developing and validating an objective neural marker of consciousness in non-communicating patients therefore presents a formidable task, since in this patient group we necessarily have no absolute reference to assess the accuracy of any determination of the presence or absence of consciousness. Consider the impact of a patient behaviourally diagnosed as vegetative, but who is in fact covertly conscious on the results of a group level connectivity study: if this patient showed intact functional connectivity, correctly indicating awareness, it would statistically *weaken* the link between consciousness (determined behaviourally) and functional connectivity, rather than highlighting the potential utility of the technique in detecting awareness. Connectivity studies undoubtedly do and will continue to be instrumental in our understanding of the neural substrates of disorders of consciousness, and they have the unique advantage of not relying on the integrity of sensory pathways or a patient's ability to understand instructions or actively participate in cognitively demanding tasks. However, their utility as diagnostic tools is currently limited by the circularity of their reference to behavioural measures. It is completely circular logic to develop tools aimed at reducing misdiagnosis while using the current diagnosis as a gauge for the accuracy of the new tools.

3. Advantages and Limitations of fMRI and EEG for the Study of DOC

Since fMRI was introduced in the early 1990's, it has had an immense impact on cognitive neuroscience research, and its use has grown exponentially, from 4 peer-reviewed fMRI publications in 1992, to about 13 *per day* in 2011 (using the same database and search terms as Logothetis, 2008). It has become a very "fashionable" technique and there are occasions when it appears to have been chosen as a research method for this reason, rather than for its suitability to a particular research question or population. This is not to minimize its importance or its contribution to cognitive neuroscience and other fields, but merely to point out that it is not the answer to every question (Logothetis, 2008). While fMRI has contributed immensely to our understanding of disorders of consciousness, and highlighted the need for brain-based tools to assess cognition and awareness in patients with DOC, it is itself clearly not the most practical solution to the problem. In order for an assessment technique to be readily adopted into standard clinical practice, it must be inexpensive, easily accessible, have few limitations in terms of patient compatibility, and be relatively simple to administer whether at the bedside, in the patient's home or care facility or in a research laboratory. fMRI and patients with severe brain injuries rarely combine to meet these criteria. Conversely, EEG is widely available, inexpensive, easy to administer at the bedside, is fairly robust to many artifacts that can cause fMRI data to be unusable, and has virtually no restrictions with regard to patient compatibility and safety. EEG is more easily validated on large groups of subjects and data acquisition times are generally shorter, making it not only more suited for clinical applications but also for the basic research required prior to applications in patients.

The potential implications for patients with disorders of consciousness, their families, and care teams, of the fMRI research described above are profound. Unfortunately, there are many, significant logistical and methodological considerations that will prevent fMRI from becoming a part of routine diagnostic assessments in standard clinical practice. The following sections will review these issues and discuss the advantages and disadvantages of employing EEG as an alternative methodology (see Table 3 for a summary).

3.1 Patient Safety and Monitoring

Many of the limitations of performing fMRI in patients with DOC are safety issues that apply to any MRI procedure in any population, but require special consideration in patients. Of particular concern for brain injury patients are implanted devices such as neurostimulators, CSF shunts, aneurysm clips, and bone flap fixation wires and clamps. Many of these devices have now been tested and deemed MR-safe at specific fields, but many are still contra-indicated or restricted (see Shellock, 2011). Some aneurysm clips are ferromagnetic and may displace and cause serious injury or death. A number of shunt valves use magnetic components and exposure to the MRI's magnetic field may change the valve settings and lead to increased intracranial CSF pressure. Some neurostimulators may malfunction, overheat, or be displaced causing injury or death. Any implanted devices and any other surgical hardware must have documented evidence of MRI compatibility for the specific model and manufacturer at the field strength of the scanner to be employed. Also, as a routine part of general MRI screening, patient background regarding previous surgeries, implants, as well as possible embedded metal such as shrapnel or bullets is required. In the case of non-communicative patients, this essential information may not be available and other, preliminary diagnostic procedures (e.g, computerized tomography, CT) may be required to rule out safety hazards prior to MRI scanning. Conversely, there are virtually no contraindications to recording EEG from the scalp surface.

The Safety Committee of the Society for Magnetic Resonance Imaging recommends that all patients who are unable to communicate should be physiologically monitored while in the scanner (Kanal and Shellock, 1992). This requires that the MR unit be equipped with specialized, MR-compatible monitoring equipment. While clinical-use MRI facilities have such equipment available, research-dedicated MRI facilities are frequently not equipped for sophisticated physiological monitoring. Monitoring is required not only for the patient's medical safety, but also for their emotional well-being. Up to 20% of patients undergoing MRI experience a claustrophobic or other distress reaction (Shellock, 2011), and may elect to terminate the scan as a result. Non-communicative patients, however, would be unable to signal such a reaction, and so should be monitored for physiological changes that might indicate distress (e.g., increased heart rate, respiration). EEG does not induce claustrophobic reactions, and requires no special monitoring.

	fMRI	EEG
Patient safety	Many implanted devices are contraindicated and pose serious safety risks.	Virtually no contraindications.
	Existing metal in body (known or unknown) poses safety risks.	No screening for metal required.
	Difficult to monitor patients for low arousal.	Low arousal easily identified on EEG.
	MRI commonly induces claustrophobic reaction, but difficult to monitor for signs of distress.	Distress from claustrophobia unlikely, but heart rate, electrodermal activity, respiration etc. can easily be monitored concurrently with EEG.
Data acquisition	Patient must be transported to specialized facility.	Can be done at patient's bedside.
	Expensive.	Inexpensive.
	Challenges in patient positioning.	Positioning rarely an issue.
	Inherent selection bias in sample due to safety, transport, and positioning issues.	Can be performed on virtually any patient.
Artifact	Large motion artifacts make entire datasets unusable.	Motion artifact can usually be corrected or rejected; exclusion of entire datasets only in severe cases.
	Implanted devices can cause severe signal loss and image distortion.	Prone to EMG artifact, but this can usually be filtered out or contaminated segments removed.
Analysis	Spatial normalization complicated by abnormal structure.	Spatial transformation not required.
	Comparison of spatial and temporal responses to normative data complicated by lesions and functional remapping.	Comparison of spatial and temporal responses to normative data complicated by lesions and functional remapping.
Interpretation	BOLD signal affected by neurovascular coupling.	Scalp EEG directly measures neural activity.
General	High levels of data loss due to safety, transport, positioning, and artifact.	Relatively low levels of data loss; due mostly to severe motion artifact.

Table 3. Summary of advantages and limitations of fMRI and EEG for the study of disorders of consciousness.

Periods of low arousal and sleep are very common in patients with disorders of consciousness. As a quality control measure, arousal should be monitored, ideally with EEG, during fMRI scanning to avoid collecting data when the patient is least likely to show activation (Laureys et al., 2004). While simultaneous EEG and fMRI recording is possible with specialized EEG equipment, it introduces a whole new set of safety concerns (see Allen, 2010 for a review), and extra analysis steps to remove gradient and ballistocardiogram artifact from the EEG data (Bénar et al., 2003). When recorded in isolation, EEG easily identifies periods of sleep, low arousal, or seizure activity, so that data can be recorded during periods of arousal, and contaminated data can easily be eliminated.

3.2 Data Acquisition

Once a patient has passed through all the necessary safety screening steps, there are still many hurdles to collecting fMRI data. Patients are often recruited from the hospital-based treatment or rehabilitation programs with which the researchers are affiliated, and scanned at the same facility. However, in cases where patients are not housed in the same facility as the scanner, specialized transport and accompanying support staff are required. Once at the scanning facility, many difficulties may be encountered in physically positioning the patient in the scanner due to muscle contractures or injuries that prevent them from lying flat and still. Though rarely mentioned in fMRI studies, data loss due to transport and positioning issues is high, which raises questions about validity of population data due to subject selection bias. EEG equipment, on the other hand, is highly portable, and patient positioning is rarely an issue making it applicable to a much wider sample of patients, even to those who are not medically stable enough to be transported or to undergo MRI scanning. In either case, we believe that it is important for studies to report the original number of candidate patients from which the final sample were drawn, and details of the reasons for excluding patients – such as transportation issues, positioning difficulties, artifact, MRI-incompatibility, etc. – so that readers can get a more accurate sense of the representativeness of the study's final sample.

3.2.1 Stimulus Delivery

Most fMRI studies in patients with DOC are conducted in the auditory modality since patients with DOC frequently have difficulty keeping their eyes open, and VS patients by definition cannot fixate on a visual stimulus. However, auditory stimulation in the very noisy scanner environment presents its own set of challenges. If data are sampled in a standard, continuous fashion, the scanner noise may interfere with the auditory stimuli, or even drown them out completely if they are not carefully titrated. The presence of scanner noise may also complicate the interpretation of results, particularly negative ones. For example, if basic auditory processing were investigated through a simple stimulus vs. rest comparison, but the stimulus generated only weak or no activation *on top of* the primary auditory activation elicited by the scanner noise, the resulting map (computed by subtracting the rest activation from the stimulus activation) would appear as though the primary auditory cortex was not functioning. For this reason, many investigators opt to employ a sparse sampling procedure (Hall et al., 1999) in which images are acquired immediately following (not during) stimulus delivery, in the period where the haemodynamic response is near its peak. Stimulus-related activation is still captured, but not contaminated by the noisy gradient switching. This technique yields better estimates of stimulus-related auditory activation but results in smaller datasets (and consequently lower statistical power) and/or considerably longer scan times, which are undesirable especially in patient groups. EEG, on the other hand, can easily be recorded during virtually any type of stimulus delivery.

3.2.2 Artifact

Undoubtedly the most problematic source of artifact in patients with DOC is motion. In almost every published group study in DOC patients, subjects have been excluded from analyses due to excessive motion artifacts. Data loss due to motion in patients with DOC is estimated at more than 25% (Adrian Owen, personal communication, 2009). Large, involuntary movements of the head or body are common, and while cushioning and light restraint may be used, movements cannot be entirely prevented from occurring in the scanner. Very small movements can be corrected during preprocessing of fMRI data, but movements of even a few millimeters can make an entire dataset unusable. Another source of artifact in brain-injured patients comes from devices implanted in the head, such as the aforementioned aneurysm clips, shunts, and neurostimulators. Even when these devices have been deemed non-ferromagnetic and completely MRI-safe, they are still foreign, usually metallic objects with different magnetic susceptibility than the surrounding brain tissue. They can create significant artifacts, loss of signal, and/or distortion of the image surrounding the object (Shellock, 2011).

EEG is also prone to certain artifacts, however these are generally correctable with little difficulty. Like fMRI, EEG is sensitive to motion, but unlike fMRI, only data recorded during the actual motion are affected. If motion is constant it becomes problematic, but occasional movements of any magnitude can easily be removed from the data without having to discard the entire dataset. EEG is also prone to EMG artifacts generated by muscles in the face and neck, for example by squinting of the eyes, grimacing, teeth-clenching, swallowing, or chewing motions. However, EMG has distinct characteristics particularly in the frequency domain and can be removed successfully, leaving the underlying EEG intact.

3.3 Analysis

Several issues arise when analyzing both structural and functional MRI data from patients with severe brain injuries. Most obvious is the issue of spatial normalization. Patients with DOC may have abnormal or deformed brain structures as a result of many factors including focal haemorrhages, hydrocephalus, shifting, craniotomy, swelling, dilated ventricles, and atrophy. This complicates transformation into stereotaxic space (e.g., Talairach space or MNI space) for group analyses or comparisons of individual patients to control subjects. The heterogeneity of injuries and their aetiologies also complicates any between-subjects comparisons. Even if normalization can be performed, it must be considered that, depending on the injury, an indeterminate amount of functional remapping may have taken place, so that functional areas may no longer correspond to the coordinates of the same functional areas in healthy controls or other patients. Given that most fMRI studies use a region-of-interest (ROI) approach to compare activations in patients to those observed in control subjects under the same conditions, the issues of normalization and functional remapping present a significant hurdle for the use of fMRI in DOC.

While EEG circumvents nearly all of the safety and data acquisition issues of fMRI, it is also prone to some of the same analysis problems as fMRI. While EEG does not require spatial normalization, functional remapping will alter the spatial distribution of signals. Temporal characteristics of EEG are also affected, often resulting in significantly delayed ERP latencies. These ERP latency shifts and unusual topographies can lead to problems in identification of ERP components. For example, the P3a and P3b components discussed in section 2.1.1 can overlap temporally, and therefore the identification of these two components relies heavily on their topographical distributions. Since both the latencies and topographies of ERPs can be altered in severe brain injury, the identification of relevant components becomes problematic. However, a set of guidelines for the recording and analysis of ERPs in clinical populations has been advanced with the goal of eliminating experimenter bias (Duncan et al., 2010). Additionally, brain injuries are often associated with marked changes in oscillatory activity, particularly in the delta and theta ranges (see Schomer and Lopes da Silva, 2010), which may complicate the interpretation of data in the frequency and time domains when comparing patients to healthy controls.

3.3.1 Interpretation

It is imperative to remember that the BOLD signal on which fMRI is based is a measure of haemodynamic response, and not a direct measure of neural activity. Neurovascular coupling is the relationship between neural activity and the haemodynamic response reflected by the BOLD signal. It is dependent upon intact signaling between neurons and blood vessels, and on the various components of vascular reactivity. Any changes to metabolic or neurotransmitter signaling, vascular tone, cerebral blood volume, blood flow, blood oxygenation, or oxygen consumption can affect the BOLD signal (Iannetti and Wise, 2007). A growing body of evidence shows that many diseases and pathologies – including brain injuries – alter neurovascular coupling and change BOLD signal without necessarily affecting neuronal function (Füchtemeier et al., 2010; Gsell et al., 2000; Krainik, et al., 2005; Lindauer et al., 2010;

Sakatani et al., 2003; 2007). In the same vein, we must also consider that patients with severe brain injuries are usually on several medications, which can also influence neurovascular coupling (Bruhn et al., 2001; Luchtmann et al., 2010; Pattinson et al., 2007; Reinhard et al., 2010). We can attribute changes in BOLD signal to changes in neural activity if and only if signaling and vascular reactivity are not altered; and we can compare between groups (e.g., patients and controls) only if these properties are the same in both groups. Therefore, the utmost caution must be used when interpreting BOLD signal in brain-injured patients, and the potential confounds in the intermediate steps of neurovascular coupling must be considered.

Conversely, EEG is a direct measure of neural activity. Currents generated by local field potentials must pass through, and are attenuated by the skull and scalp before reaching sensors on the scalp surface but the signal recorded directly reflects the brain's electrical activity, and is not dependent upon the many components of neurovascular coupling. Therefore, the degree of inference required to interpret EEG-based measures is substantially reduced compared to fMRI. Naturally, the effects of medication must also be considered with EEG, however only drugs that act on the CNS are of major concern since neurovascular coupling is not a factor in EEG.

3.4 Prognostic Value

Findings from fMRI studies of cognition and consciousness all have one thing in common. There is enormous variability in the type and amount of activation that patients show under the same conditions, even within the same diagnostic category. The question becomes whether there is some significance to this variability in terms of the patients' likely outcome. Clinically, this would be one of the most useful pieces of information that could be extracted from fMRI. Most studies state prognosis as one of the main goals of brain research in disorders of consciousness, however only two fMRI studies have systematically examined it. In 2008, Di et al. systematically reviewed 15 fMRI and PET studies that included a total of 48 VS patients. They classified the results from all patients according to whether they showed no activation; typical, low-level activation of primary sensory cortices; or higher-level activation of associative cortices that is 'atypical' for VS. They observed that atypical, higher-level associative cortex activation predicted recovery of consciousness in the cases they analyzed with 93% specificity and 69% sensitivity. Coleman et al. (2009) found an equally encouraging result when they examined the correspondence between level of auditory processing in their 22 VS and 19 MCS patients (study described above in section 2.1.2). They classified the level of activation observed in each patient as 1: no response to sound, 2: low-level response to sound only, 3: mid-level response to speech stimuli, and 4: high-level response to semantic aspects of speech. This score was compared to each patient's score on the Coma Recovery Scale – Revised (Giacino et al. 2004) that was measured at the time of testing and 6 months later. The analysis revealed a strong correlation (r = 0.81) between the level of auditory activation and the CRS-R score 6 months post-testing – despite a non-significant correlation between auditory activation and CRS-R at time of testing. These two studies provide strong evidence that fMRI could offer valuable prognostic information, however the selection bias inherent in fMRI studies of DOC (see section 3) limits the generalizability of such findings.

A considerable body of literature exists on the predictive value of evoked potentials and ERPs in coma. A full review is beyond the scope of this paper, but a meta-analysis found that the N100, the MMN, and the P300 are all significant predictors of outcome following severe brain injury (Daltrozzo et al., 2007). The interested reader is referred to recent reviews (Duncan et al., 2011; Folmer et al., 2011; Guerit et al., 2009; Vanhaudenhuyse et al., 2008). However, only a few studies have produced preliminary prognostic data for VS and MCS. Kotchoubey et al. (2005) found that the presence of an MMN was related to better outcome in VS patients, and Cavinato et al. (2009) observed a positive relationship between the P300 and outcome from VS.

4. Conclusion

Over the past decade or so, fMRI has lent new insight into disorders of consciousness, and together with EEG has revealed that a small proportion of patients diagnosed as vegetative or minimally conscious have a much greater conscious awareness than they are able to indicate through behaviour. fMRI has helped to highlight the inadequacies of current diagnostic tools, and set the stage for the further development of brain-based, behaviour-independent measures of cognition and consciousness. However, it is difficult to argue that fMRI is well suited for use in this population. The logistics of simply putting these patients in an MRI scanner are prohibitive, before even discussing issues of data quality and interpretation. Ultimately, the goal of using technology like fMRI in this context is to reliably detect those cases where the patient possesses conscious awareness that cannot be detected through behavioural measures, and to facilitate some form of communication. Identifying patients with signs of conscious awareness is critically important because it opens the door to existing and highly effective rehabilitation interventions for a group of people who historically have been judged as incapable of benefitting from such interventions. However, if the technology we have chosen to use can only be applied to a small subset of MRI-compatible and cooperative patients, we are not much closer to having a practical clinical tool. While researchers should always carefully consider which methodology is best suited to address their specific research questions, EEG is overall a more widely applicable, less expensive, more readily available, and more practical technique for application in patients with DOC, and research in the field is quickly evolving away from fMRI and back to EEG-based measures.

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CHAPTER 2: BALLISTOCARDIOGRAM CORRECTION IN SIMULTANEOUS EEG/FMRI RECORDINGS: A COMPARISON OF AVERAGE ARTIFACT SUBTRACTION AND OPTIMAL BASIS SET METHODS USING TWO POPULAR SOFTWARE TOOLS.

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Preface

Chapter 1 provided a comprehensive overview of the use of fMRI and EEG for the assessment of cognition and awareness in disorders of consciousness, and ended with a discussion of the relative merits and drawbacks of each method for this population. EEG is clearly a preferable method in this case and the current trend in DOC research reflects a shift from fMRI to EEG-based methods. However, there has been an implicit assumption that EEG and fMRI would be equally able to detect awareness in an individual patient; that if a VS-diagnosed patient is covertly conscious, EEG and fMRI would be equally likely to spot the misdiagnosis. Each method in isolation has been able to detect awareness in otherwise non-responsive patients (Connolly et al., 1999; Cruse et al., 2011; A. M. Goldfine et al., 2011; Monti et al., 2010; Owen et al., 2006), but there has never been reported case where both methods were used in the same patient. The goal in shifting from fMRI to EEG is to be able to apply the method to a larger number of patients and thus possibly detect more cases of covert awareness in misdiagnosed VS. However, fMRI and EEG measure very different brain processes (haemodynamic response and electrical activity, respectively) so it is possible that they would not lead to the same diagnosis in an individual patient. In that case, switching from fMRI to EEG may forfeit valuable information. Therefore it is imperative to establish the degree to which the two methodologies converge upon a conclusion about an individual's state of awareness. This was the central goal of the study presented in Chapter 3. The only way to perform such a comparison while ensuring that the underlying brain state is identical, and not influenced by factors such as the substantially different testing environments, arousal, attention, learning, or practice effects, is to record them simultaneously in the same subjects. Thus, simultaneous EEG/fMRI is the only suitable methodology for this purpose. While simultaneous EEG/fMRI recordings have been performed and published for well over a decade, the two techniques are profoundly incompatible and many technical obstacles must be overcome in order to achieve reasonable data quality. Essentially, a sensitive system designed to detect and amplify minute, microvolt-level variations in electrical activity via metallic sensors and long, conductive cables is placed inside powerful magnetic fields, both static and rapidly changing, with strengths about 60,000 times stronger than the Earth's magnetic force to which it is normally exposed. The electrodes and leads are also exposed to intense radio-frequency (RF) energy emitted during the scan sequence (Lemieux et al., 1997). Equipment and participant safety issues have mostly been resolved through the development of specialized MRI-compatible EEG recording systems (see Gutberlet, 2010 for review). However, in accordance with Faraday's Law, any change in the magnetic fields induces currents in the electrodes and leads. This includes switching of the magnetic gradients (Allen et al., 2000), subject movement, cable movement/vibration (Masterton et al., 2007), and motion related to the cardiac cycle (Allen et al., 1998; Debener et al., 2008). The voltage potentials resulting from these currents are recorded along with the EEG and form artifacts that are orders of magnitude greater than the EEG in both amplitude and rate of change (Allen et al., 2000; Ritter et al., 2007). The result is a recorded signal in which the EEG is completely obscured by artifact. Subject and cable motion-related artifacts can be reduced by carefully stabilizing the subject and the equipment inside the scanner (Mullinger et al., 2013), and the RF artifact is effectively suppressed with a low pass filter since it has a much higher frequency range than the EEG. This leaves the artifacts caused by the gradient switching and by the cardiac cycle. As this chapter will discuss, the gradient artifact can be effectively removed with the proper hardware configuration and acquisition parameters because of its technical origin (Mandelkow et al., 2006; Mullinger et al., 2013). However, the cardiac-related artifact, known as the ballistocardiogram (BCG), is endogenous to the subject and can fluctuate substantially over time (Debener et al., 2008). Its removal has been the subject of many investigations in the signal processing literature, with little consensus on the most effective method. The validity of the results of the simultaneous EEG/fMRI study presented in Chapter 3, which forms the core of this thesis, hinged upon effective removal of this artifact. Therefore, a great deal of preliminary analysis was performed to ensure the quality of the BCG removal. Of the many BCG removal procedures that have been proposed (e.g., Assecondi et al., 2009; Dyrholm et al., 2009; Ellingson et al., 2004; Masterton et al., 2007; Nakamura et al., 2006; Srivastava, et al., 2005; Vincent et al., 2007; Wan et al., 2006), only two (Allen et al., 1998; Niazy et al., 2005) have been 'packaged' and made available to other researchers. No direct comparison of the two software tools has previously been published, and so it was of vital importance to the integrity of the study presented in Chapter 3 that the performance of each method be established. The current chapter presents a detailed analysis of the performance of two popular and widely available algorithms for removal of BCG.

Abstract

Electroencephalography (EEG) data recorded during functional magnetic resonance imaging (fMRI) acquisition are subject to large cardiac-related artifacts that must be corrected during post-processing. The present study compared two widely used ballistocardiogram (BCG) correction algorithms as implemented in two software programs. The algorithms were compared on reduction of BCG amplitude, correlation of corrected data with electrocardiogram (ECG) traces, correlation of independent components with ECG traces, and event-related potential (ERP) signal-to-noise ratio. Both algorithms effectively reduced the BCG artifact, with a slight advantage of average artifact subtraction (AAS) over the optimal basis set (OBS) method when the quality of the correction was examined at the individual subject level. This study provides users of these software tools with an important, practical and previously unavailable comparison of the performance of each method.

1. Introduction

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are two of the most popular research methods for examining brain function. Each method has strengths and weaknesses for addressing particular empirical questions, and these are often complementary – for example, fMRI has high spatial resolution (on the order of millimeters) where EEG has much lower spatial resolution due to the distortion of the brain's electrical signal as it passes through the tissue and bone between the neural generators and the electrodes that record the signal. Conversely, EEG has high temporal resolution (on the order of milliseconds) where the temporal resolution of fMRI is relatively low (on the order of seconds) due to the sluggish nature of the haemodynamic response that underlies the blood oxygen level dependent (BOLD) signal. As a result, the combination of these two techniques provides extremely valuable information that is not achievable with either method in isolation. Recent developments in EEG acquisition hardware and data processing methods have made the simultaneous recording of EEG and fMRI a safe and viable method for investigating brain processes at a spatially and temporally fine-grained level, and for investigating the relationships between electrophysiological and haemodynamic correlates of brain processes. Simultaneous EEG-fMRI has been applied in several domains including the localization of seizure foci in epilepsy (see Cunningham et al., 2008; Laufs & Duncan, 2007; Moeller et al., 2013 for reviews), investigations of the neural generators of spontaneous EEG oscillatory activity (e.g., Feige et al., 2005; Goldman et al., 2002; Gonçalves et al., 2006; Laufs et al., 2003; Moosmann et al., 2003; Omata et al., 2013), and studies of fMRI correlates of sleep stages (see Maquet, 2010 for review), among other applications.

There are, however, numerous obstacles to the collection of electrophysiological data inside a strong magnetic field with rapidly changing gradients. While most of the safety issues have been resolved with the advent of MRI-compatible EEG systems, substantial problems related to data quality and artifact remain a challenge for researchers. Many of these can be minimized by careful control of data collection procedures (Gutberlet, 2010; Mullinger et al., 2013), but there are two types of artifact that are unavoidable and must be corrected during post-processing. These are the scanner artifact caused by the magnetic gradient switching during fMRI acquisition, and the ballistocardiogram artifact related to the cardiac cycle.

1.1 Gradient Artifact (GA)

Because EEG records electrical signals from the brain, the electrodes and leads are necessarily made of conductive materials. In accordance with Faraday's law of induction, changes in the magnetic fields induce currents in the electrodes and leads. During echo-planar (EPI) fMRI acquisition, rapid switching of magnetic gradients occurs as each slice is imaged. This gradient switching is reflected in the EEG as a fast-rising, transient signal with a slew rate that can be on the order of millivolts per millisecond, that completely obscures the underlying EEG (Figure 1). Therefore, in order to properly characterize the GA, the EEG must be sampled at significantly higher-than-normal rates. The GA contains high-frequency components not fully covered even with a sampling rate of 5 kHz and so minimal deviations in the timing of the EEG and fMRI cause variability in the sampling of the artifact, making removal challenging. However, advances in hardware have enabled the synchronization of the clocks of the EEG and MRI devices, eliminating this technical challenge when the hardware is available. The

GA is present in the EEG over a broad spectrum, including typical EEG frequency ranges of interest (<100 Hz) and so cannot be removed by filtering alone (Felblinger et al., 1999). However, since the gradient artifact is a purely exogenous technical artifact which does not vary over time, it can be very successfully be removed using a simple average template subtraction approach with subsequent adaptive filtering, when the EEG and MRI clocks have been synchronized (Mandelkow et al., 2006). In this approach, a sliding average artifact is calculated over a fixed number of epochs – an epoch typically being either a volume or a slice acquisition – then subtracted from the EEG for each epoch. The artifact subtraction is followed by the implementation of an adaptive noise cancellation filter (Allen et al., 2000) to remove residual imaging artifact. The data are also typically low-pass filtered and downsampled for subsequent processing. The gradient artifact from a single slice of EPI can be seen, before and after GA correction, in Figure 2.

1.2 Ballistocardiogram (BCG) Artifact

Once the gradient artifact has been removed, a second major source of artifact, the ballistocardiogram, can be observed in the EEG (Figure 3). The BCG is a periodic distortion in the EEG that is related to the cardiac cycle and is always present when the subject is within the scanner's magnetic field. The artifact causes a peak in the frequency spectrum at the heart rate frequency (normal range 1-1.7 Hz) and several higher harmonics (Vanderperren et al., 2007). The BCG therefore also falls within the range of interest for EEG and so cannot be removed by filtering. While the exact origins of the BCG are not conclusively known, several possible mechanisms have been proposed.

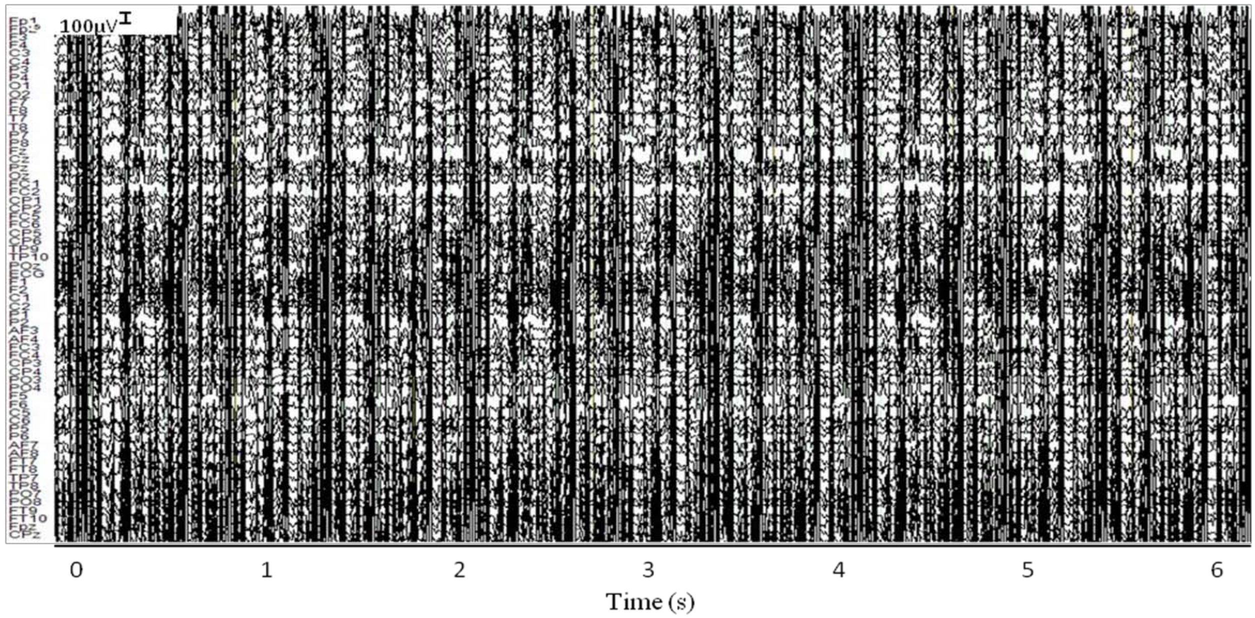

Figure 1. A 6-second segment of raw EEG data collected during simultaneous fMRI, dominated by gradient artifact.

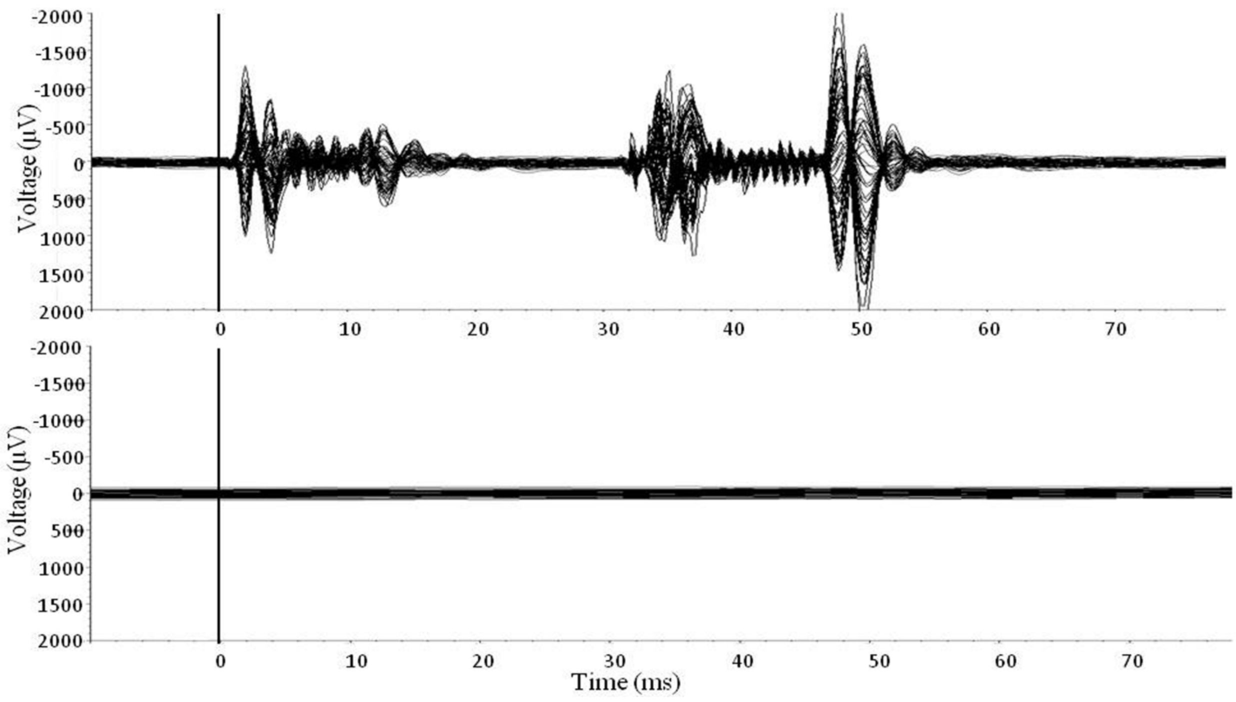

Figure 2. Gradient artifact from a single slice of EPI. The top panel shows the artifact in all channels overlaid, and the bottom panel shows the same segment of data after GA correction.

Fundamentally, all of the proposed mechanisms are underpinned by the basic principles of electromagnetism that dictate that movement of conductive materials in a magnetic field causes electromagnetic induction. Head rotation caused by heartbeat, pulsatile motion of the scalp caused by expansion of blood vessels, and the flow of blood – itself a conductive medium – through vessels adjacent to the scalp have all been proposed as possible sources of the BCG (Debener et al., 2008). The BCG is much less straightforward to remove than the GA because it is influenced by both endogenous (cardiovascular system) and exogenous (scanner) variables that alter the temporal and spatial characteristics of the artifact. Heart rate and blood flow vary over time, affecting the temporal properties of the signal. Also, because the sources of the BCG are spatially non-stationary, the artifact has a moving, rotating, and polarity-inverting topography, and these effects as well as the magnitude of the BCG are increased at higher field strengths (i.e., 3T or 7T vs. 1.5T; Debener et al., 2008).

Many methods have been proposed to remove the BCG(Allen et al., 1998; Assecondi et al., 2009; Benar et al., 2003; Bonmassar et al., 2002; Dyrholm et al., 2009; Ellingson et al., 2004; Mantini et al., 2007; Masterton et al., 2007; Nakamura et al., 2006; Niazy et al., 2005; Sijbers et al., 2000; Srivastava et al., 2005; Vincent et al., 2007; Wan et al., 2006) however two methods have become widely used and are implemented in popular software, accessible to a breadth of researchers with and without extensive expertise in signal processing. The average artifact subtraction (AAS) procedure based on Allen et al. (1998) builds an artifact template for each channel separately using a sliding average of cardiac events identified in concurrently recorded ECG. This template is then subtracted from the EEG. This method is implemented in BrainVision Analyzer (BVA; Brain Products, GmbH, Germany). The optimal basis set

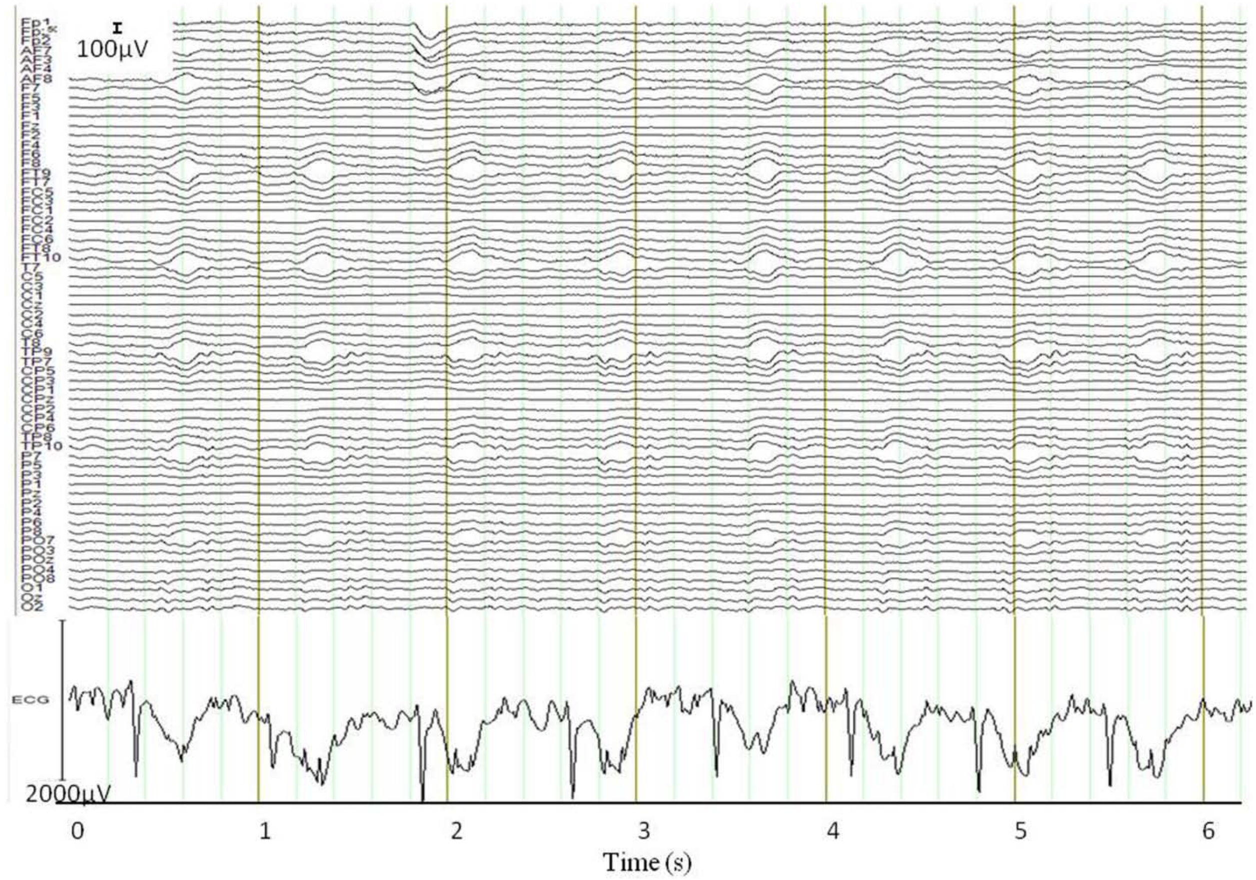

Figure 3. The same segment of data as Figure 1, following gradient artifact correction. The BCG is clearly visible in the EEG traces.

(OBS) method of BCG removal (Niazy et al., 2005) uses temporal PCA on each channel in order construct a basis set which is then used to regress out the BCG artifact from the EEG. This method has the advantage of allowing for more variability between repetitions of the artifact to be accurately captured. OBS is implemented in the FMRIB plug-in (University of Oxford Centre for Functional MRI of the Brain) for the EEGLAB toolbox (Delorme & Makeig, 2004) in Matlab (The MathWorks, Inc., USA). These two methods use quite different approaches to deal with artifacts found in the EEG signal due to the MRI environment, but the only comparison of these two methods is contained in the paper introducing the OBS method (Niazy et al., 2005), and gives no information about how the AAS procedure was implemented, making the comparison opaque to the reader. Additionally, Niazy et al. (2005) used combined adaptive thresholding with QRS peak correction to detect heart beats before BCG removal with OBS and AAS. However, the BrainVision Analyzer implementation of AAS uses a simpler method of detecting heart beats by thresholding correlation with a template heart beat. Presumably, the different detection algorithms also influence the accuracy of the OBS and AAS methods. The objective of the current study, therefore, was to compare the effectiveness of these two widely used BCG correction algorithms as implemented in BrainVision Analyzer and the FMRIB plugin. Such a comparison appears overdue particularly as more laboratories explore the utility and complexities of simultaneous EEG and fMRI recording for various applications and seek to make an informed choice of correction algorithm from those already available for general use.

2. Methods

2.1 Data Acquisition

Data were acquired from 4 healthy volunteers (2 female), ages 21-30 years (mean = 24.25; SD = 4.03), who had normal or corrected-to-normal vision, and no history of audiological, neurological, or psychiatric disorder. The protocol was approved by the local research ethics board and all participants provided written informed consent.

EEG data were collected using a BrainAmp MR system (Brain Products, GmbH, Germany), including a 64-channel MR-compatible BrainCap (Brain Products, GmbH, Germany) containing sintered Ag/AgCl electrodes positioned according to the standard 10/20 system, with the ground electrode at position AFz, and the reference at FCz – the standard configuration of the BrainCap MR (Brain Products, GmbH, Germany). One additional channel was attached to the mid-back along the left paravertebral line to record the ECG. All electrode impedances were maintained below 10 kΩ with an abrasive electrolyte paste. EEG was sampled at 5 kHz and applied to a 0.1-250 Hz bandpass filter. Sampling was synchronized to MRI gradient onset by SyncBox (BrainProducts, GmbH, Germany) to facilitate removal of gradient artifact.

FMRI data were acquired on a GE Signa Excite 3T MRI, with a 32-channel receive-only head coil. Functional images were acquired with a GRE EPI sequence with ASSET in 40 axial slices, 4 mm thick, no gap, 3200 ms TR, 35 ms TE, 90° flip angle, 240 mm FOV, 64 x 64 matrix.

The EEG/fMRI data were obtained from a mental imagery study during which subjects were presented with a single word in both auditory and visual modalities using Presentation software (Neurobehavioral Systems, USA), which served as a cue for the subject to perform a pre-defined mental imagery task. The visual words were presented in white text on a black background in the center of a projection screen mounted on the MRI head coil. Auditory stimuli were pre-recorded and presented through MR-compatible, noise-attenuating headphones. Stimuli were presented every 16 seconds (5 TR) and were synced to scan onset via a TTL pulse from the scanner. Auditory stimuli were presented 100-150 ms after the onset of the accompanying visual stimulus. For the present purpose, event-related analyses were calculated to the onset of the visual stimulus. Two runs of 42 trials each were recorded inside the scanner.

One additional 42-trial run was recorded outside the scanner. In order to keep recording conditions as similar as possible to those inside the scanner, patients lay supine on a bed with their head in a coil similar to the one used in the scanner. Stimuli were presented with the same method used in the scanner, with the exception that subjects viewed the visual stimuli on a computer screen via a mirror attached to the head coil rather than projected onto a screen. The EEG were data recorded with identical parameters. The order of in/out recording was counterbalanced. In order to compare equal quantities of data for in vs. out, only the first run of the data acquired inside the scanner were analyzed for the present study.

2.2 Data Analysis

2.2.1 Gradient Artifact Removal

Gradient artifact removal was performed using the averaged artifact subtraction method (AAS; Allen, Josephs, & Turner, 2000) as implemented in BrainVision Analyzer 2.0 (Brain Products, GmbH, Germany), with a sliding template averaged over 21 artifact periods. Data were subsequently downsampled to 500 Hz. Data recorded outside the scanner underwent downsampling only.

2.2.2 AAS Pulse Artifact Correction

BrainVision Analyzer 2.0 (Brain Products, GmbH, Germany) was used to detect cardiac events and to remove the BCG artifact with the AAS method (Allen et al., 1998). R-peak detection results were manually inspected for accuracy and detection parameters readjusted until all R-peaks in the ECG trace had been accurately detected. AAS was subsequently performed using a sliding average of 21 artifacts.

2.2.3 OBS Pulse Artifact Correction

The FMRIB plug-in (University of Oxford Centre for Functional MRI of the Brain) for the EEGLAB toolbox (Delorme & Makeig, 2004) for Matlab (The MathWorks, Inc., USA) was used to detect cardiac events and remove pulse artifact with the OBS method (Niazy et al., 2005). The detection phase is not adjustable by the user. For the correction phase, an optimal basis set of 3 principal components was employed per Niazy et al. (2005).

2.2.4 Evaluation

The performance of each pulse artifact correction method in each subject was compared on the following criteria:

(1) Pulse artifact amplitude: EEG data were segmented from 100 ms before to 500 ms after each cardiac event detected in the ECG by each method (R-peaks in the case of AAS, and QRS-complexes in OBS). These segments were then averaged and the peak-to-peak amplitude of artifact, averaged across channels, was compared before and after each correction method (Mantini et al., 2007). This analysis will provide an estimate of the reduction in artifact amplitude by each method.

(2) Correlation between EEG and ECG traces: Pearson's correlations were calculated for each EEG channel in relation to the ECG trace, before and after each correction method. This analysis will give an estimate of the amount of residual BCG signal in the individual channel traces with a linear relationship to the ECG.

(3) Correlation between independent components (ICs) and ECG trace: Extended infomax independent components analysis was carried out in BrainVision Analyzer 2.0 on the corrected data. Correlations between the resulting ICs and the ECG trace were calculated (Debener et al., 2007; Srivastava et al., 2005). This analysis will consider both spatial and temporal information to provide an estimate of the amount of independent activity related specifically to the residual BCG.

(4) ERP signal-to-noise ratio (SNR): The SNR was calculated using BrainVision Analyzer's built-in option. The SNR is estimated statistically by first calculating the total power as the mean squares of all data points. The noise power is then calculated as the square of the difference between each data point and its corresponding value in the averaged signal. The signal power is quantified as the difference between the total power and the noise power. Finally, the SNR is estimated as the average signal power over the average noise power. This analysis will give insight into the effect of each correction method on the detection of underlying EEG signal.

3. Results

3.1 Pulse Artifact Amplitude

The pulse artifact amplitudes in the uncorrected individual subject data ranged from 32.35±14.37 μV (Subject D with FMRIB detection) to 94.44±41.14 μV (Subject B with BVA detection) (Table 1 and Figure 4a). The average amplitude of the artifacts detected by BrainVision Analyzer was consistently larger than of those detected by the

FMRIB plugin, but only by a small margin in 3 subjects. Subject C, however, showed a more substantial difference of 16.73 μV. This observation suggests that the BVA algorithm (aided by the user-adjustable detection parameters) was slightly more accurate at placing the markers, so that the amplitude of the artifact was preserved during averaging; an interpretation confirmed by visual inspection of the cardiac markers. However, since the FMRIB plugin does not include any user-adjustable parameters, it could not be improved upon.

The amplitude of the same average signal after correction, representing residual BCG, ranged from 0.05±0.02 μV (Subject D after AAS) to 1.91±0.99 μV (Subject C after OBS). Both the amplitude and the variability of the residual artifact were consistently higher after OBS correction with the FMRIB plugin than after AAS correction with BVA (range 0.04 to 1.2 μV higher in amplitude and 0.02 to 0.48 μV higer in SD; Figure 4b). This result suggests that the AAS algorithm left less residual BCG in the EEG.

	Before correction		After correction		Percent reduction (%)	
Subject	BVA detection	FMRIB detection	BVA (AAS)	FMRIB (OBS)	BVA (AAS)	FMRIB (OBS)
A	52.16 ±29.70	50.47±28.93	0.07±0.04	0.25±0.11	99.87	99.50
B	94.44±41.14	93.68±40.91	0.12±0.06	0.82±0.38	99.87	99.12
C	78.73±36.87	62.00±27.30	0.71±0.51	1.91±0.99	99.10	96.91
D	33.88±14.91	32.35±14.37	0.05±0.02	0.09±0.04	99.85	99.73
Group	64.80±30.65	59.62±27.88	0.24±0.16	0.77±0.38	99.63	98.71

Table 1. Pulse artifact amplitudes for cardiac events before and after correction, using each algorithm's respective detection and correction procedures. BVA = BrainVision Analyzer; AAS = average artifact subtraction; OBS = optimal basis set.

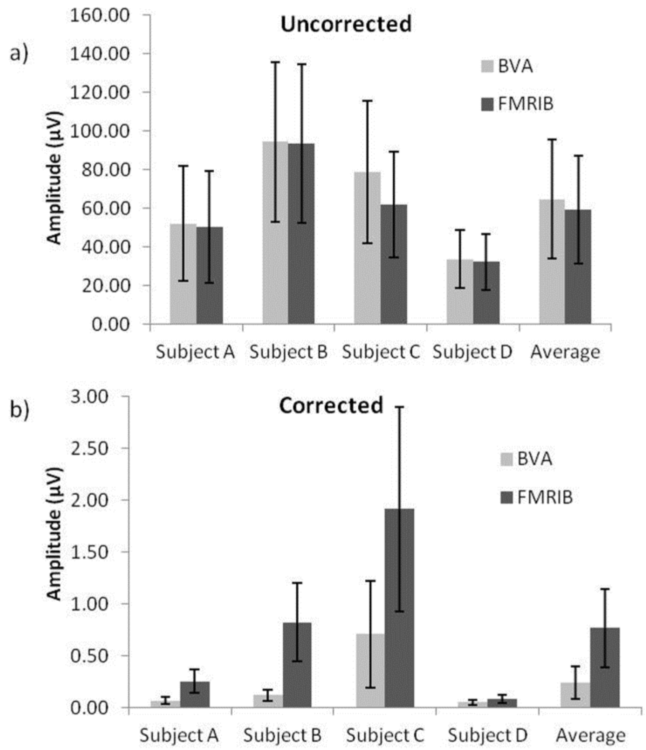

Figure 4. BCG peak-to-peak amplitudes before and after correction. a) amplitudes of the averaged BCG as identified by each program's pulse artifact detection procedure. b) amplitudes of the averaged BCG following correction with each program's corresponding artifact removal procedure. Error bars represent standard deviation.

3.2 Correlations Between EEG and ECG

The difference between the OBS and AAS correction that was visible in the residual BCG amplitudes was not apparent in the correlations between the EEG and ECG signals. The correlations were very nearly identical at both the individual channel (Figure 5) and the average levels (Figure 6) in all subjects.

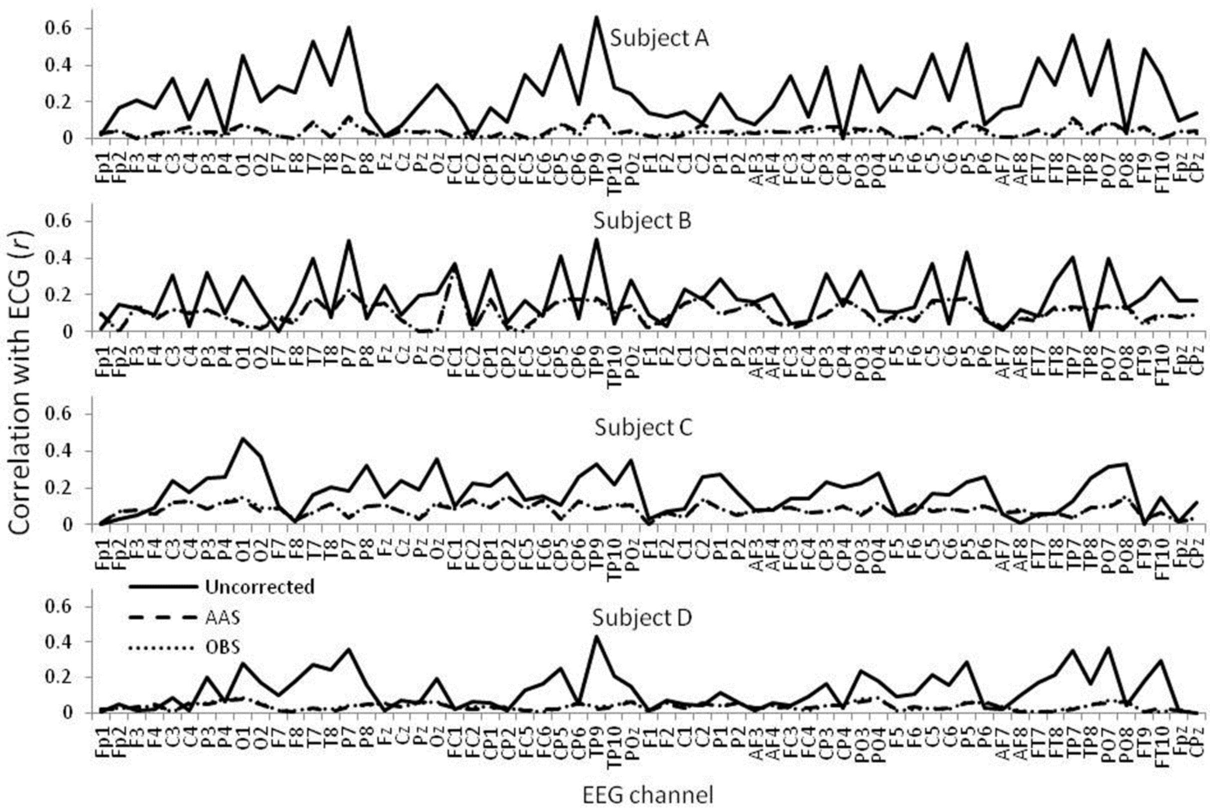

Figure 5. Correlations between ECG and EEG before and after BCG correction.

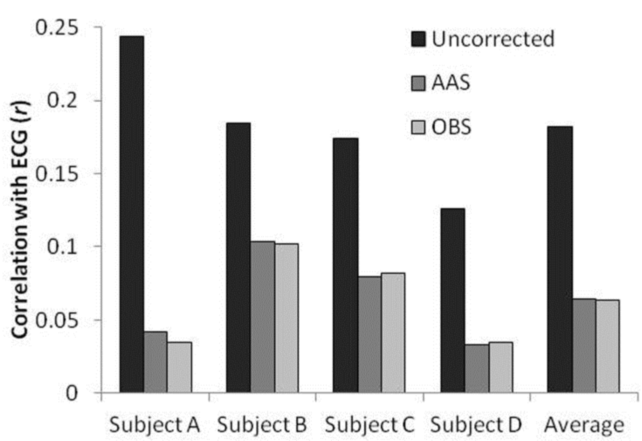

Figure 6. Correlations between EEG and ECG before and after BCG correction, averaged across channels.

3.3 Correlations Between Independent Components and ECG

Mantini et al. (2007) and Srivastava et al. (2005) observed a division in correlation values between ICs and ECG whereby components containing BCG artifact fell above a threshold of approximately $r = 0.25$, while components unrelated to BCG fell well below. Thus $r < 0.25$ was adopted as the threshold for the current evaluation. Correlations between independent components and ECG were reduced to sub-threshold levels in subjects A, C, and D by both the AAS and OBS corrections (Figure 7). In subject B, 3 components after AAS and one component after OBS exceeded the threshold, suggesting that the BCG had not been effectively removed by either algorithm. This is consistent with the higher values for the correlations between the EEG and ECG also observed in this subject (Figures 5 and 6).

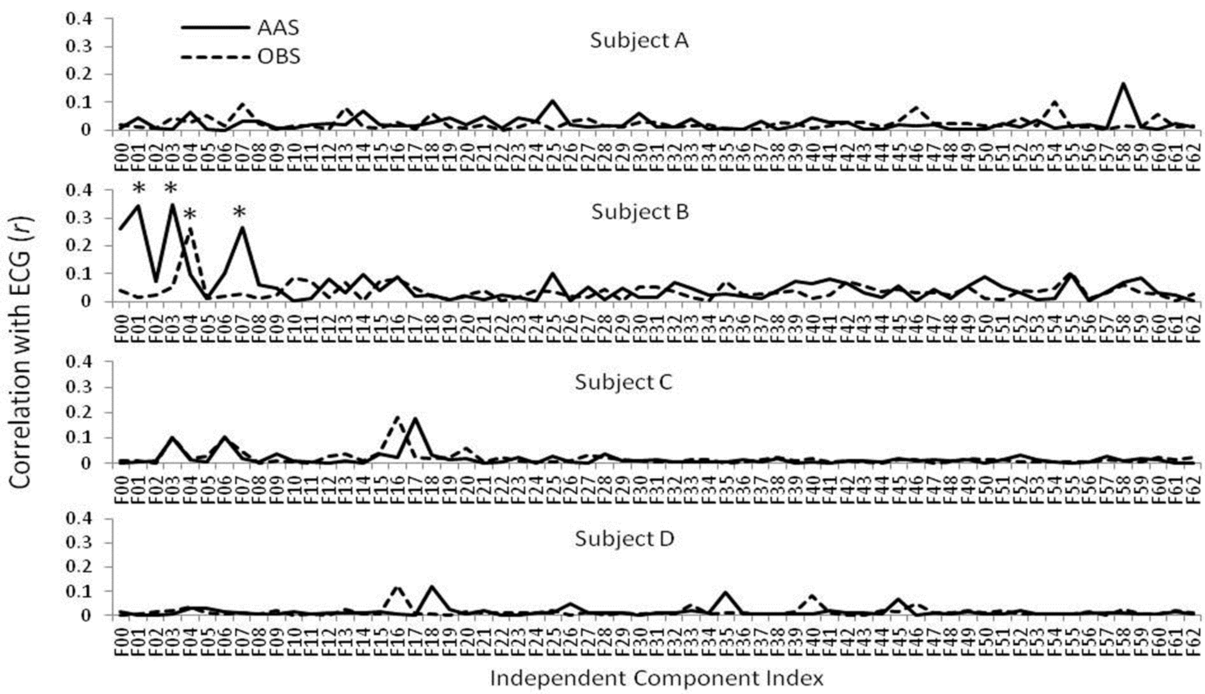

Figure 7. Correlations between independent components and ECG after correction with AAS and OBS. * $r > 0.25$.

3.4 ERP Signal-to-Noise Ratio

EEG channel Cz was chosen as the channel of interest for this analysis since the N1 ERP, a component of the typical response to visual stimulation that appears as a negative voltage peaking between 100-200 ms post-stimulus, was readily identified in all subjects at this site in the data from both inside and outside the scanner (Figure 8).

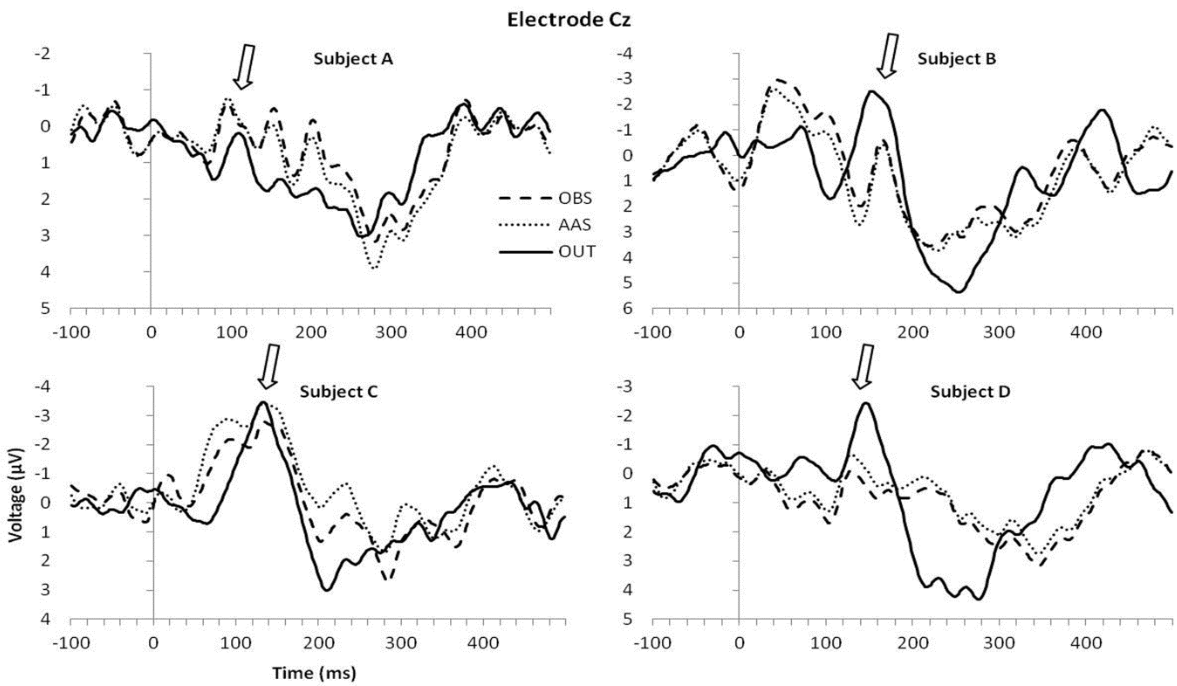

Figure 8. N1 ERP waveforms at EEG site Cz recorded outside the scanner (OUT) and during simultaneous fMRI acquisition, corrected for BCG with AAS and OBS.

In all subjects, the estimated SNR was lower in the ERPs recorded during simultaneous fMRI than in those from outside the scanner (mean reduction in SNR = 55%). When averaged across subjects, the SNR values for the two methods were within an absolute difference of 0.001 of each other. However, at the individual subject level, AAS resulted in higher ERP SNR in three out of four subjects, with only one subject showing higher SNR following OBS (Figure 9).

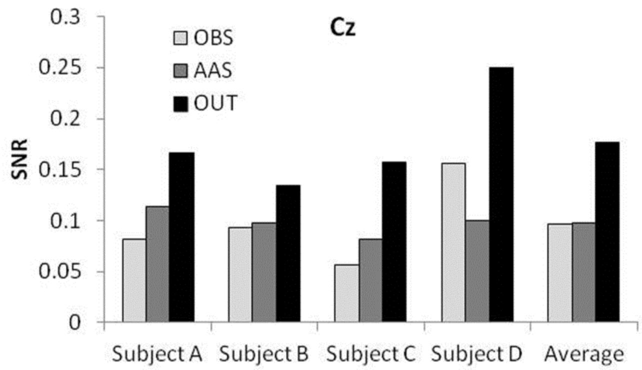

Figure 9. Signal-to-noise ratio (SNR) at channel Cz for ERPs calculated to visual stimulus onset from data collected outside the scanner (OUT), and from data collected inside the scanner and corrected for BCG with AAS and OBS.

4. Discussion

As simultaneous EEG-fMRI recording becomes more widely used by researchers from a variety of disciplines, it is important to assess the effectiveness of popular artifact correction algorithms that are accessible to users with no specialized skill in signal processing. The current study compared the BCG correction algorithms of two popular EEG processing software programs – one commercially available (BrainVision Analyzer, Brain Products GmbH, Germany) and the other a freely downloadable plugin (FMRIB; University of Oxford Centre for Functional MRI of the Brain) for the freely downloadable EEGLAB toolbox (Delorme & Makeig, 2004) for Matlab (The MathWorks, Inc., USA).

Both methods reduced the amplitude of the BCG by >96%. AAS performed better than OBS in terms of artifact amplitude reduction, both overall and in a majority of subjects. There were no differences between the two methods with regards to the correlation between EEG and ECG following correction, indicating that differences between the methods were not evident in the linear relationship between the recorded ECG and the individual EEG channels. When spatial information is taken into account in the ICA analysis, the correlation between BCG and the ICA components was reduced in three of four subjects by both methods to well below threshold levels. In a fourth subject, three components remained above threshold after AAS, while only one component was above threshold after OBS, suggesting that while neither method had successfully removed all of the artifact, the OBS did a better job of separating out more independent components related to the BCG. The ERP SNR in the data acquired simultaneously with fMRI was substantially lower than SNR of ERPs acquired outside the scanner. Reduced SNR inside the scanner could be attributable to a variety of factors including residual scanner artifact and BCG, and more general motion-related artifact. EEG recorded simultaneously with fMRI is extremely susceptible to motion artifact, and while data containing large movement artifacts can be manually removed from the data, subthreshold artifacts may still be present and contribute to overall noisier data. Additionally, since both the GA and the BCG lie within the frequency range of interest for EEG, it is possible that the correction algorithms remove some of the EEG signal in addition to the artifact, thereby reducing the signal in addition to the increased noise. No difference was observable in the averaged SNR between OBS and AAS corrected data, however, 3 out of four subjects showed higher SNR after AAS than OBS.

This was a small sample and only a subset of the myriad possible data characteristics was examined. However, both methods performed approximately equally in the present context and effectively removed the vast majority of the BCG. AAS showed a slight advantage in terms of artifact amplitude reduction and ERP SNR.

Debener et al. (2007) propose an additional step in which ICA components containing residual BCG artifact following OBS are removed before data reconstruction. This could equally be applied following AAS. However, as with any ICA-based approach to artifact removal, a substantial amount of user knowledge about the characteristics of specific artifacts is required to ensure accurate performance, thereby introducing an element of subjectivity.

An important question for applications in patient populations is how well each method can handle noise. Most pathological groups produce noisier data sets, for a variety of reasons. OBS would inherently seem to have an advantage over AAS in that it does not assume a temporal relationship between different instances of artifact. However the placement of cardiac peak markers is an important step in the removal of BCG and the BrainVision implementation of AAS has the advantage of a user-adjustable detection procedure to ensure accurate detection of cardiac peaks before the artifact removal stage. It remains an empirical question how well each of these methods perform in the presence of less than ideal data quality. For applications in healthy individuals, however, researchers can be confident in the application of either method for the removal of BCG, as long as the quality of the correction is monitored in each subject.

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CHAPTER 3: EEG AND FMRI AGREE: MENTAL ARITHMETIC IS THE EASIEST FORM OF IMAGERY TO DETECT.

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Preface

Simultaneous EEG and fMRI recording is a technically intensive technique that is susceptible to many artifacts - the most problematic of which were discussed in Chapter 2 - and requires substantial setup time. These factors, combined with the additional limitations on performing fMRI in DOC patients (see Chapter 1), made the use of DOC patients for this study of the convergence of fMRI and EEG measures of awareness prohibitive, if not impossible. An alternative approach to the question, which could be implemented in healthy volunteers, was required. Since these subjects would be aware, addressing the question of whether fMRI and EEG provide the same information about level of awareness became more challenging. Functional neuroimaging-based judgments about level of awareness in DOC are based on the detectability of brain activation during an intentional mental task, such as imagery. Individuals vary in both their subjective ability to perform imagery tasks and in the amount/consistency of activation that they generate during these tasks (Cui et al., 2007; Herholz et al., 2012; Lorey et al., 2011; Olivetti Belardinelli et al., 2009). Therefore, the question was reformulated to investigate whether EEG and fMRI provide the same information about the relative amount of activation generated by a subject during a variety of mental imagery tasks. This also provided the opportunity to examine whether the amount of activation was related to a person's familiarity with the activity being imagined; knowledge that could guide the selection of appropriate imagery tasks for use in individual DOC patients. Chapter 3 presents the core findings of this thesis.

Abstract

The diagnosis of disorders of consciousness (DOC) by traditional behavioural methods is problematic because a patient may be aware but unable to produce the required behaviour to indicate their state. Researchers are developing methods of detecting voluntary mental activity using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in order to eliminate the reliance on behaviour for diagnosis. Mental imagery has been a favoured means to this end, but only a small number of potential imagery tasks have been investigated. Additionally, because of the many difficulties in using fMRI in patients with DOC, an increasing number of studies are employing EEG. However, there has been no verification that these two modalities provide converging information at the individual subject or group level. The present study used a variety of mental imagery paradigms during simultaneous EEG and fMRI recording to accomplish 3 main objectives: to determine whether one mental imagery task generates the most robust activation across subjects or whether this varies by individual; to investigate whether the robustness of activation can be predicted from familiarity with the imagined activity; and whether EEG and fMRI converge upon the same conclusions about individual imagery performance. Results indicated that mental arithmetic generates the most robust activation; that level of activation cannot be predicted from familiarity; and that fMRI and EEG do converge upon the same answers to these questions.

Introduction

Severe brain injury, when survived, typically results in a period of coma – a state of total unresponsiveness in which the eyes remain closed. If the patient does not awaken and recover responsiveness, coma is replaced after 10-30 days by a vegetative state (VS; Jennett & Plum, 1972; Posner et al., 2007), also known as unresponsive wakefulness syndrome (UWS; Bruno et al., 2011; Gosseries et al., 2011; Laureys et al., 2010). In VS/UWS, patients exhibit periods of eye-opening resembling sleep-wake cycles but still show no evidence of conscious awareness (Royal College of Physicians Working Group, 2003; The Multi-Society Task Force on PVS., 1994). Alternatively (or subsequently) a diagnosis of minimally conscious state (MCS) may be accorded if the patient demonstrates reproducible signs of intentional behaviour (Giacino et al., 2002), implying some level of conscious awareness. The distinction between VS/UWS and MCS is a critical one that has implications for treatment, rehabilitation, pain management, and end-of-life decisions (Boly et al., 2008; Bressman & Reidler, 2010; Fins & Shapiro, 2007; Schnakers et al., 2012; Schnakers & Zasler, 2007; Wilkinson et al., 2009). However the accurate diagnosis of disorders of consciousness (DOC) presents a unique set of challenges. Consciousness is a subjective experience and therefore can only be unequivocally established in an individual if they can indicate that this is indeed the case. Clinical assessments employ protocols designed to elicit these behavioural indications of consciousness by probing behaviours ranging from reflexive to intentional response to command. If a patient is unable to produce a level of response consistent with conscious awareness (i.e., purposeful behaviour) they are diagnosed as VS/UWS. However, this behaviour-based system of diagnosis is intrinsically flawed: a patient may possess some level of awareness but be unable to produce a response or understand the instructions requesting them to do so, for any number of reasons such as motor impairment, sensory or perceptual impairment, aphasia, seizure activity, low arousal, and pain (Giacino et al., 2009). Locked-in syndrome (LIS) presents the most extreme example of this scenario. Patients with total LIS are fully conscious but are completely paralyzed and as a result not able to generate the behavioural responses necessary to indicate consciousness (American Congress of Rehabilitation Medicine, 1995).

A growing body of research has sought to circumvent the reliance on behavioural measures by instead observing brain activity using functional neuroimaging measures such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). A variety of paradigms have been used to assess cognitive functions from basic sensation and perception to language comprehension in patients with disorders of consciousness (see Harrison & Connolly, 2013 for a full review). However, in order to argue that a particular brain response provides evidence for conscious awareness, it must be established that the activation is a result of the patient's intentional performance of the task in question and cannot be attributable to automatic processes that may occur in the absence of conscious awareness. One method of achieving this end, that has gained traction for its simplicity and its demonstrated effectiveness at detecting covert awareness (e.g., Cruse et al., 2011; Goldfine et al., 2011; Monti et al., 2010; Owen et al., 2006), is mental imagery. The subject is simply asked to imagine performing an activity such as playing tennis, navigating around their home, or moving a hand or foot. The brain activity during the imagery periods is then compared to a resting baseline or to another imagery condition, and if consistent, differential activation is detected, it is concluded that the subject is willfully performing the requested imagery task.

The application of mental imagery for the detection of awareness was initially developed with fMRI (Bardin et al., 2011; Boly et al., 2007; Monti et al., 2010; Owen et al., 2006). However the use of fMRI in patients with disorders of consciousness presents a number of practical obstacles which limit its use to a small subset of patients (see Harrison & Connolly, 2013 for a discussion). As a result, DOC researchers have followed the lead of researchers using mental imagery in brain-computer-interfaces for patients with severe motor and neuromuscular disorders (see e.g., Neuper et al., 2006; Wolpaw et al., 2002 for reviews) and adopted EEG as a more affordable, accessible, and widely applicable method (Cruse et al., 2011; Goldfine et al., 2011).

Objectives and Research Questions

The present study addresses two outstanding issues in the field. The first is that the imagery tasks employed with DOC have been limited to sport imagery (tennis or swimming), navigation imagery, and hand/foot movement imagery. The sport and navigation imagery conditions are based largely on a single study (Boly et al., 2007) which found that navigation imagery was more robust than subvocal rehearsal in one group of subjects, and that tennis imagery was more robust than face imagery in another group. The tennis and navigation paradigms were subsequently used to demonstrate awareness in a single VS/UWS patient (Owen et al., 2006) and became the standard for research in DOC. A recent application of hand and foot movement imagery in VS/UWS (Cruse et al., 2011) was based on the foundations of brain-computer interface research using these tasks for control of devices (see Neuper & Pfurtscheller, 1999; Neuper et al., 2006a; Neuper et al., 2006b; Wolpaw et al., 2002 for reviews). We believe that, while this small set of imagery tasks has proven effective in many cases, further investigation of alternative imagery tasks is merited. Pilot studies with both healthy and brain-injured participants have shown that individuals vary substantially in their subjective ability to perform specific mental imagery tasks (unpublished observations). Evidence from fMRI studies of vividness of mental imagery in various modalities suggest that there is a relationship between an individual's subjective rating of imagery performance and the magnitude of the blood-oxygen level dependent (BOLD) response (Cui et al., 2007; Herholz et al., 2012; Olivetti Belardinelli et al., 2009). These findings suggest that while navigation, sport, or hand/foot imagery can successfully demonstrate awareness in patients who are easily able to perform them, there may be a subset of patients who have difficulty engaging in a particular imagery task and are not able to generate brain activation robust enough to be detected. Our study sought to broaden the search for useful mental imagery tasks in several ways. First, we added imagery conditions that have not been examined in this context previously. Second, we examined all of the imagery conditions in the same group of subjects so that the robustness of activation could be directly compared across all conditions within individuals. Third, and perhaps most significantly, we defined robustness of activation in a spatially agnostic fashion that is critical if the technique is to be applied in patients with brain injury (Goldfine et al., 2011). Previous fMRI studies (Boly et al., 2007; Monti et al., 2010; Owen et al., 2006) have adopted a region-of-interest (ROI) approach based on previous imagery studies and on control group data. This type of analysis is legitimate and widely used to increase statistical power, but is insufficient for the present purpose of developing a method for direct application to brain injured patients. A catastrophically injured brain cannot be expected to produce a pattern of activation comparable to that observed in healthy controls, even if the associated function remains. A great deal of functional remapping may take place as a result of brain injury, so activation is probed only in those locations where it occurs in healthy brains, evidence of intact function may go undetected (Carmichael, 2003; Kolb, 2003; Wittenberg, 2010). The current study examines instead the consistency of response within an individual, rather than comparing patterns of activation to a normative group. For EEG this took the form of a machine-learning based approach which finds the data features most relevant to the separation of imagery versus rest in an individual subject. For fMRI, a whole-brain conjunction analysis was employed to identify regions that are consistently active within an individual over repeated testing runs. Within the overarching goal of expanding the range of mental imagery paradigms, we sought to answer three specific questions:

Research Question 1: Is There an Imagery Task that Provides the Most Robust Activation Regardless of Individual Differences?

It is not sufficient to simply identify additional mental imagery tasks that may be useful for the detection of awareness. It is important to determine whether there are individual differences in response to imagery tasks that elicit the most robust brain activation, or whether one task consistently stands out as the most robust in all subjects. This information would guide the choice of imagery paradigms for the assessment of awareness. For example, if one paradigm is consistently the most robust in healthy subjects, it could be applied in DOC patients with some confidence that if the task is being actively performed, the resulting activation will be detectable. If, however, there is substantial individual variability in which task produces the most robust activation, then we must either employ a variety of imagery paradigms, or somehow predict the task that will generate the most robust activation for that individual. The present study addresses this question by comparing a variety of imagery tasks, within individuals, on measures of electrophysiological and haemodynamic brain responses.

Research Question 2: Can Robustness of Activation Be Predicted from Ratings of Task Familiarity?

If individuals vary on which imagery condition produces the best activation, we must then ascertain whether, in order minimize the number of paradigms necessary, the best imagery task for a given patient can be chosen based on their individual abilities or interests. FMRI studies have shown a relationship between vividness of mental imagery and the magnitude of the BOLD response (Cui et al., 2007; Herholz, et al., 2012; Lorey et al., 2011; Olivetti Belardinelli et al., 2009). However, in patients with disorders of consciousness, these ratings are not available. The choice of imagery task for such a patient would therefore be based on what type of activity they are likely to be able to imagine most vividly. Logically, this would be an activity that they are familiar with performing. For example, an athlete might be asked to imagine playing their sport, whereas a musician might be asked to imagine a piece of music, or to imagine the finger movements associated with playing their favourite instrument. It is not known, however, whether a person's familiarity with an activity increases the vividness of their imagery and/or the intensity of the brain response during imagery. The present study addresses this question by investigating the relationships between subjective ratings of imagery vividness and familiarity with the imagined activity. This relationship will be examined in relation to the fMRI and EEG responses recorded during imagery.

Research Question 3: Do fMRI and EEG Provide Converging Answers to Questions 1 and 2?

The third and most important goal of this study was to determine if EEG and fMRI produce the same answers to the above questions. There has been a shift in the field of disorders of consciousness from a focus on fMRI to an almost exclusive use of EEG for the detection of awareness. However, there has been an implicit assumption that if an individual patient is performing a mental imagery task, the brain activity will be equally detectable by EEG and fMRI and either of the two techniques would ultimately lead us to the same conclusion about a patient's level of awareness. But fMRI and EEG measure two very different indices of brain activation (Logothetis, 2008) and so it is entirely possible that the two methodologies would lead us to different conclusions about an individual patient. It is also possible that the convergence or divergence of the two methods is different for various imagery paradigms. For example, a motor imagery paradigm may generate activation that is easily distinguishable from rest with both fMRI and EEG, while music imagery may be more easily detected by fMRI than EEG, or vice versa. Given the shift away from fMRI and toward EEG, it is imperative to verify that we are not losing anything 'in translation'. The only way to test this empirically is to record both types of data and compare their ability to distinguish imagery from rest at the individual subject level. In order to directly compare fMRI and EEG data, we must be certain that the underlying brain states are *identical* during both recordings. The data must therefore be recorded *simultaneously*, and not sequentially, in the same subjects in order to rule out the influence of extraneous variables like arousal, attention, learning, etc. The present study examines the questions posed above (individual variability in robustness of activation for various imagery tasks, and relationship of activation to task familiarity) in both EEG and fMRI, recorded simultaneously to determine the degree to which the two techniques converge.

Methods

Participants

Data were collected from 17 healthy volunteers (11 female) aged 18-48 years ($\bar{x}$ = 26.5, SD = 8.7) who had no history of neurological, psychiatric, or audiological disorder. Data from 2 subjects were excluded due to excessive motion artifact, and one subject was excluded due to susceptibility artifact in the fMRI data caused by dental metal. Seven subjects were excluded due to an as yet undiagnosed technical problem with their fMRI data. The fMRI data exhibited a pattern such that the first seven subjects showed appropriate activation during the imagery tasks with expected amounts of within- and between-subject variability, but the last seven subjects showed virtually no activation after the conjunction analysis (see 'fMRI Analysis' section below) with individual runs exhibiting lack of activation or suspicious noise patterns. This resulted in a significant difference in the number of active voxels between the first half of the subjects and the second half, $t(82) = 3.983$, $p < .001$. As a result, we concluded that the data from the last 7 subjects did not belong to the same distribution as the first 7 and were therefore not of sufficient quality to be included in the current study. The study protocol was approved by the local research ethics board and all participants provided written informed consent.

Experimental Design and Procedure

Data were acquired in three (3) runs of simultaneous EEG/fMRI recording. Each run consisted of six (6) 16-second trials in each of 7 different conditions:

1) Sport-related motor imagery. Participants were asked to choose the sport or full-body activity (e.g., dancing, jumping jacks) that is most familiar to them, and to imagine performing that activity intensely, focusing on the kinesthetic and somatosensory aspects of that activity rather than on visual aspects.
2) Navigation imagery. Participants were asked to imagine navigating around their home from room to room, paying attention to all aspects of the room (e.g., placement of furniture, decor, objects in room).
3) Music imagery. Participants were asked to choose a song that was very familiar to them, and were asked to imagine listening to that song through headphones, concentrating on all aspects of the song, including the melody, the instrumentation, the rhythm, the lyrics, and the vocals (if present), etc.
4) Mental arithmetic. Participants were asked to choose a different 3-digit number at random for each trial and count backwards by threes.
5) Finger tapping imagery. Subjects were asked to imagine pushing a button with each of the fingers of the right hand in succession, repeatedly, focusing on the somatosensory and kinesthetic rather than visual aspects of the imagery.
6) Running imagery. Similar to the sport imagery condition only in this case subjects were asked to imagine running. This task was chosen as a standard imagery condition of an activity with which all subjects would have some level of familiarity.

7) Rest. Participants were asked to clear their mind and think of nothing in particular.

Each trial began with a single-word auditory cue, presented through headphones, consisting of a single pre-recorded word indicating which of the 7 conditions was to be performed for the duration of the trial. Participants were asked to keep their eyes open and fixate on a central target, in order to avoid excessive eye movements, alpha EEG associated eye closing, and sleepiness. Conditions were presented in pseudo-random order, with no condition occurring more than twice in a row. These conditions were explained in detail before subjects entered the scanner.

fMRI Acquisition

fMRI data were acquired on a GE Discovery MR750 3T MRI with an 8-channel receive-only head coil. Functional images were acquired with a GRE EPI sequence with ASSET in 40 axial slices, 4 mm thick; 3200 ms TR, 35 ms TE, 90° flip angle, 240 mm FOV, 64 x 64 matrix. 214 volumes were acquired per functional run and the first four volumes of each run were discarded to allow for T1 equilibration.

Whole-brain high-resolution 3D anatomical images were acquired with an FSPGR sequence with ASSET in 1 mm-thick axial slices; 240 mm FOV, 512 x 248 matrix.

EEG Acquisition

EEG was recorded with an MR-compatible 64-channel system (Brain Products GmbH, Munich, Germany) with electrodes at standard 10-20 sites, referenced to site FCz with ground electrode at AFz. EEG was sampled at 5 kHz with a 0.1-250 Hz bandpass filter. Electrode impedances were kept below 10 kΩ. EEG sampling was synchronized with the MRI system's clock via SyncBox (Brain Products GmbH).

Imagery Questionnaire

Following testing, participants were asked to fill out a questionnaire about their subjective experiences performing each of the imagery tasks. The questionnaire was adapted from the Mental Imagery Questionnaire – Revised (MIQ-R; Hall & Martin, 1997) and the Vividness of Movement Imagery Questionnaire-2 (VMIQ-2; Roberts et al., 2008). Subjects rated each condition on their familiarity with the actual activity involved and the vividness of their imagery of that activity.

fMRI Analysis

All fMRI analyses were carried out in Brain Voyager QX 2.6 (Maastricht, Netherlands). Functional image preprocessing included slice scan time correction, 3D motion correction, and high-pass temporal filtering. Statistical parametric maps were computed from the preprocessed data using a multi-run, single-subject general linear model (GLM) with the 6 mental imagery conditions as predictors, and the rest condition as baseline, with separate predictors for each run. A conjunction contrast was computed for each condition to identify only those voxels that were active for that condition across *all three runs*. The resulting map was thresholded at $p < 0.01$, and corrected for multiple comparisons to $p < 0.05$ using a cluster threshold estimation procedure (Forman et al., 1995). The total number of positive active voxels in the surviving clusters was tallied for each condition in each subject.

EEG Preprocessing

EEG data were corrected for MRI gradient artifact using an average artifact subtraction procedure (Allen, Josephs, & Turner, 2000) as implemented in BrainVision Analyzer 2.0 (Brain Products, GmbH, Germany). Data were downsampled to 500 Hz. Cardiac events were detected in the concurrently recorded ECG using BrainVision Analyzer's detection algorithm. Ballistocardiogram artifacts were corrected with the optimal basis set (OBS) approach (Niazy, Beckmann, Iannetti, Brady, & Smith, 2005) as implemented in EEGLAB (Delorme & Makeig, 2004) with the R-peak markers imported from BrainVision Analyzer. Ocular artifacts were corrected with ICA. A Butterworth zero-phase IIR filter was applied with bandpass 1-70 Hz, with a 60 Hz notch filter and data were digitally re-referenced to a common average. Each imagery trial was segmented into four 3.5-second epochs, beginning 2 seconds after the onset of the instruction, in order to avoid any responses specific to the auditory instruction stimulus. Segments were rejected if a) two adjoining data points differed by more than 50 μV, b) a difference of more than 200 μV was observed in a 200 ms interval, or c) the absolute amplitude exceeded 100 μV. Brain region sources were estimated on the concatenated segments for each condition with BESA Research 6.0's (BESA, GmbH, Germany) brain source montage which estimates, from the 64-channels of EEG, 3 orthogonal sources at each of 15 brain regions, for a total of 45 sources.

Machine Learning Based Analysis

If a paradigm is to be applied in severely brain-injured populations, it is crucial that the analysis method assesses differences in EEG activity conditions without relying on criteria established on normative groups. A severely injured brain may not produce the same patterns of activation as a healthy one, so the analysis method must be able to detect differences between conditions, when they exist, solely on the basis of their consistency within the individual. For this reason we chose a machine learning approach to classify each imagery condition versus rest in each subject. For each subject, the machine learning procedure was carried out 6 times – once for each imagery condition: sport, navigation, music, math, finger tapping, and running, each compared to rest. The training set in each case consisted of 72 EEG epochs from each of 2 conditions (imagery or rest) for a total of 144 epochs (minus any that were rejected for artifact). The training set also included the condition label corresponding to each epoch (type of imagery, rest). The machine learning procedure consists of the following phases: feature calculation, feature selection, classifier training and validation of the resulting model. Each of these phases is described briefly below. The reader is referred to Khodayari-Rostamabad et al. (2010), Khodayari-Rostamabad et al. (2013), and Ravan et al. (2011) for more detailed descriptions of the machine learning process.

Feature Calculation

The first phase of the machine learning process consists of the calculation of a set of candidate features from each epoch of EEG data. For this study, the set of candidate features consisted of power spectral density (PSD) parameters for each brain region, and magnitude coherence values between all possible pairs of brain regions. Both are calculated over a spectrum of 1-30 Hz in 1 Hz increments. These were calculated using Matlab's (The MathWorks, Inc., USA) 'mscohere' and 'cpsd' functions, respectively. These functions use a modified Welch periodogram method (Welch, 1967) incorporating a Hamming window for PSD and coherence estimation. Coherence values inherently range from -1 to 1, and PSD values were normalized to have zero mean and variance = 1.

Feature Selection

The feature calculation step results in an extremely large number of candidate features, most of which will have little or no relationship to the target variable (imagery vs. rest). We therefore select those features that have minimum mutual statistical dependence (redundancy), and simultaneously, maximum statistical dependence (relevance) with respect to the imagery condition, to yield a much smaller set of N_r most discriminating features. To this end, we used the minimal-redundancy-maximal-relevance (mRMR) algorithm proposed by Peng, Long, and Ding, (2005), which uses a mutual information criterion to quantify statistical dependence. In our case, N_r ranged between 1 and 10 features. The result of the feature selection process is a set of M vectors, where M is the number of training samples, each of length N_r. The vectors each correspond to a point in N_r-dimensional feature space. Ideally the points would form two tight and non-overlapping clusters in the feature space, corresponding to the two conditions. In reality, however, the clusters overlap to varying degrees, creating classification error.

Classifier Training and Validation

The next phase of the machine learning process is the training of a classifier and evaluation of its performance. Normally, this is done by a training process followed by a testing process on a separately acquired dataset. However, because of the limited number of sample trials we could acquire, we used a cross-validation process to evaluate the classification rate achievable with a machine learning method. In the cross validation process, training is coupled with testing; specifically, a leave-one out (L1O) cross-validation procedure was used. In the L1O procedure, one epoch at a time is removed from the training set and the feature selection and classifier specification algorithms are carried out on the remaining data. Then the resulting classifier is tested on the omitted epoch and its accuracy recorded. This process is repeated until all epochs have been omitted once, and the accuracy of the classifier over all iterations is tallied.

The purpose of the classifier is to take the feature vector for a given epoch and predict whether that epoch belongs to the imagery condition or to the rest condition. We implemented this process with a support vector machine (SVM; Cortes & Vapnik, 1995) using Matlab's 'svmtrain' and 'svmclassify'. In order to find the optimal classification model (which is specified by a set of parameter values, such as the type of kernel function, and the value of the parameters C, σ), the L1O cross validation was run multiple times, in each of which a different set of parameter values was used. In the end, the best classification model is determined as that which corresponds to the lowest overall L1O error rate. First a linear kernel function was applied, and repeated with a range of values for C, which controls the soft margin, ranging from 0.25 to 8. The soft margin allows a degree of error in the division of the two classes, but chooses a hyperplane that divides the points in feature space as neatly as possible. The SVM L1O procedure was repeated with a radial-basis function (rbf) kernel, which has an additional parameter, σ. The rbf-SVM was applied iteratively with the same set of C values employed in the linear case, and with values of σ ranging from 0 to 8. This entire classification procedure was performed iteratively using 1 to 10 features to identify the combination of parameters that yielded optimal classifier performance.

Because the machine learning procedure is designed to find structure in the data under adverse conditions, classification accuracies above 50% can be achieved by chance on purely random data. In order to verify that the accuracy rates returned by the machine learning procedure were above a rate that could be achieved by chance, we employed a permutation-test (jack-knife) approach. For each subject and each imagery condition, half of the feature vectors from each of the two conditions entered into the classifier (one of the imagery conditions vs. rest) were chosen at random and assigned the label for the opposite condition, resulting in two groups of feature vectors each containing half imagery and half rest. These new groups were then entered into the machine learning algorithm with the same parameters that yielded the highest classification accuracy in the non-randomized analysis. This procedure was repeated 100 times for each condition, for each subject yielding a distribution of output values that could be attributable to chance. The result of the non-randomized machine learning procedure was deemed to be above chance if it was greater than 95% of the values obtained with the randomized labels.

Statistics

In order to address Research Question 1 – whether one (or more) imagery conditions are consistently associated with stronger fMRI or EEG signal, or whether the strength of activation by condition varies between individuals, repeated measures analyses of variance (ANOVAs) were performed separately for fMRI and EEG data. Because our interest is in the relative ranking of each imagery condition within an individual, rather than differences between the group mean number of voxels activated or EEG classification accuracy for each condition, a non-parametric approach was applied. Friedman's ANOVA (Friedman, 1937, 1939) is based on ranked data: the 6 imagery conditions for each individual are ranked from 1 (lowest) to 6 (highest) and the test statistic is calculated from the ranks rather than the original data. This approach also has the benefit of not relying on the satisfaction of parametric assumptions. If one (or more) of the imagery conditions consistently gives better imaging results across subjects, a significant result is expected. If subjects vary in terms of which imagery condition produces the best activation, a non-significant result is expected.

In order to address Research Question 2 – whether robustness of activation to imagery can be predicted from a participant's level of familiarity with the activity being imagined - linear regression analyses were performed with ratings of familiarity as predictors for EEG classification accuracy and number of active fMRI voxels, respectively, across all imagery conditions. To verify whether our data replicate previous findings of a relationship between vividness of imagery and strength of brain activation (Cui, et al., 2007; Herholz et al., 2012; Lorey et al., 2011; Olivetti Belardinelli et al., 2009), a second linear regression was performed separately for fMRI and EEG with ratings of vividness as a predictor. Finally, to verify our assumption that ratings of familiarity would be related to ratings of imagery vividness and therefore, based on previous findings (Cui, et al., 2007; Herholz et al., 2012; Lorey et al., 2011; Olivetti Belardinelli et al., 2009) be predictive of brain activation, Pearson's correlation was calculated between the two ratings across all imagery conditions.

Research question 3 was addressed by qualitative comparison and evaluation of the EEG and fMRI results from questions 1 and 2.

Results

Research Question 1: Is There an Imagery Task that Provides the Most Robust Activation Regardless of Individual Differences?

fMRI

The first question we sought to address was whether individuals vary in terms of which imagery conditions produce the most robust activation, or whether one (or more) task consistently and robustly differs from rest in all subjects.

Subject	Math	Navigation	Sport	Fingers	Music	Running
A	1557	746	16	335	81	0
B	789	599	620	423	112	0
C	551	108	11	373	35	0
D	1156	758	37	137	75	0
E	2563	374	1079	130	38	24
F	585	681	339	277	294	60
G	206	21	134	36	20	0
Mean	1058	470	319	244	94	12

Table 1. Number of positive voxels for each imagery condition vs. rest, in order of average number, in the statistical parametric map of the 3-run conjunction analysis.

Analysis of the fMRI data revealed that one condition stood out as consistently most robust. The results of the conjunction analysis showed the highest number of active voxels in the mental math condition in 6 out of 7 subjects as well as in the group mean. In the 7th subject, it produced the second highest number of active voxels. There was also a condition that produced the least activation across all subjects. Running imagery elicited the smallest number of active voxels in all 7 subjects, in fact failing to produce any reliable activation in all but 2 subjects. Statistical parametric maps for the three-run conjunction analysis in a sample subject are shown in Figure 1. The number of active voxels for each condition is shown for each subject in Table 1 and Figure 2. The rank of each imagery condition is shown for each subject in Table 2.

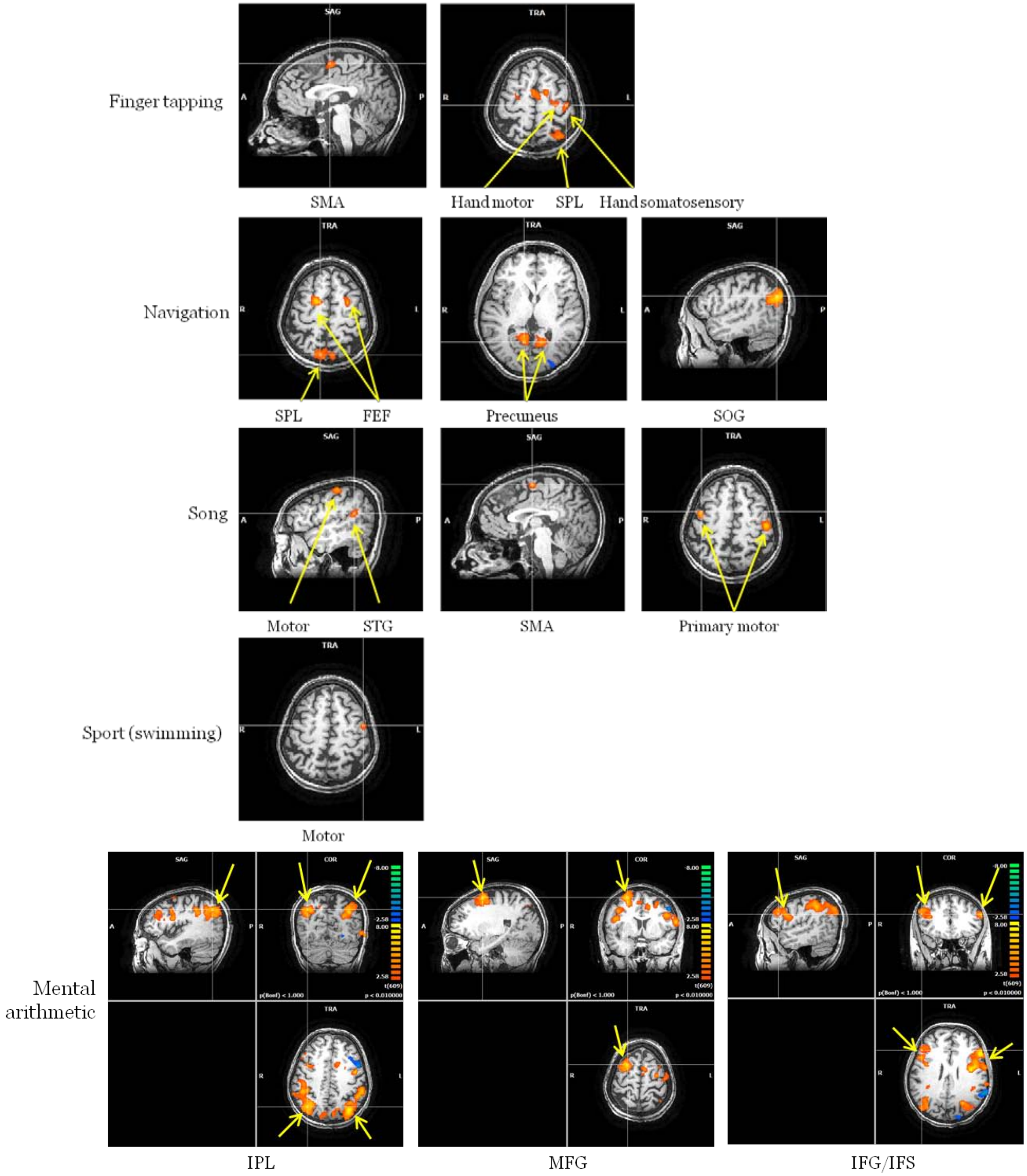

Figure 1. Statistical parametric maps of the three-run conjunction analysis for each imagery condition in a sample subject. Running is not shown because there were no

active voxels in the map. SMA: supplementary motor area; SPL: superior parietal lobule; FEF: frontal eye fields; SOG: superior occipital gyrus; STG: superior temporal gyrus; IPL: inferior parietal lobule; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; IFS: inferior frontal sulcus.

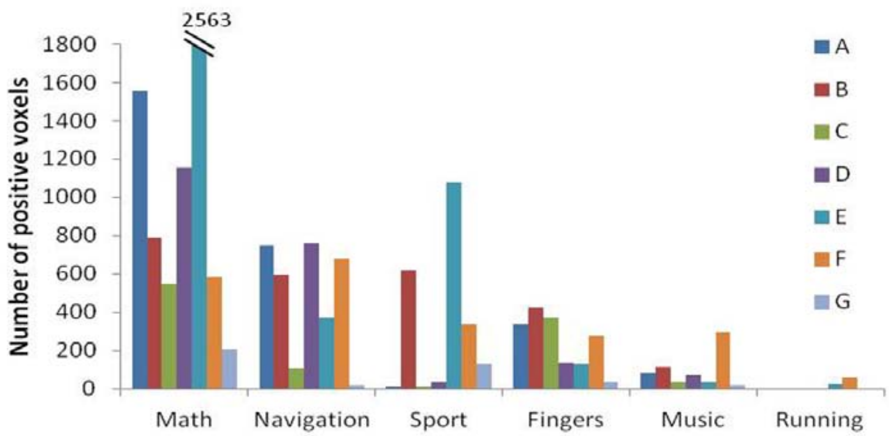

Figure 2. Number of positive fMRI voxels for each imagery condition vs. rest in the statistical parametric map of the 3-run conjunction analysis for each subject.

Subject	Math	Navigation	Sport	Fingers	Music	Running
A	6	5	2	4	3	1
B	6	4	5	3	2	1
C	6	4	2	5	3	1
D	6	5	2	4	3	1
E	6	4	5	3	2	1
F	5	6	4	2	3	1
G	6	3	5	4	2	1
Mean	5.86	4.43	3.57	3.57	2.57	1.00

Table 2. Rank of number of active fMRI voxels for each imagery condition in each subject. 6 = highest rank; 1 = lowest rank.

Friedman's ANOVA showed a significant effect of imagery condition, $\chi^2(5) = 27.08$, $p < .001$. Since Math had the highest mean rank (5.86), post hoc Wilcoxon's signed rank test was used to compare Math to each of the other imagery conditions.

After Bonferroni correction for multiple comparisons, the difference between Math and Navigation approached significance, $z = -2.20$, $p = .08$, and the differences between Math and all other conditions were significant, $z = -2.37$, $p < .05$.

EEG

The classification accuracies obtained from the machine learning procedure ranged from 59.6% to 93.0% (Table 3). Only 3 of these did not meet the criterion for better-than-chance performance: Subject C, Sport, Subject E, Running, and Subject G, Sport, fell below the 95th percentile on the distribution of accuracies returned by the permutation test.

The pattern in the EEG classification rates was somewhat less clear than in the fMRI activation. When ranked by group mean classification accuracy, Fingers scored highest (80.6%) and Running scored lowest (69.7%; Table 3, Figure 3). However, when the individual ranks were examined, the Math condition again produced the highest classification accuracy rates in a majority of subjects (4 out of 7), and ranked in the top two in 6 out of 7 subjects.

Subject	Fingers	Math	Navigation	Sport	Music	Running
A	79.9	72.7	72.5	68.8	74.8	78.0
B	72.2	77.8	72.9	73.6	69.0	69.2
C	93.0	72.3	67.8	59.6*	60.6	68.1
D	81.2	84.9	90.6	77.0	72.7	67.6
E	83.1	83.8	76.8	80.0	72.5	61.7*
F	85.0	90.6	90.0	89.9	81.4	77.9
G	69.7	73.8	64.1	59.9*	61.6	65.0
Mean	80.6	79.4	76.4	72.7	70.4	69.7

Table 3. EEG classification accuracy (%) for each imagery condition vs. rest. * Failed to meet better-than-chance performance criterion.

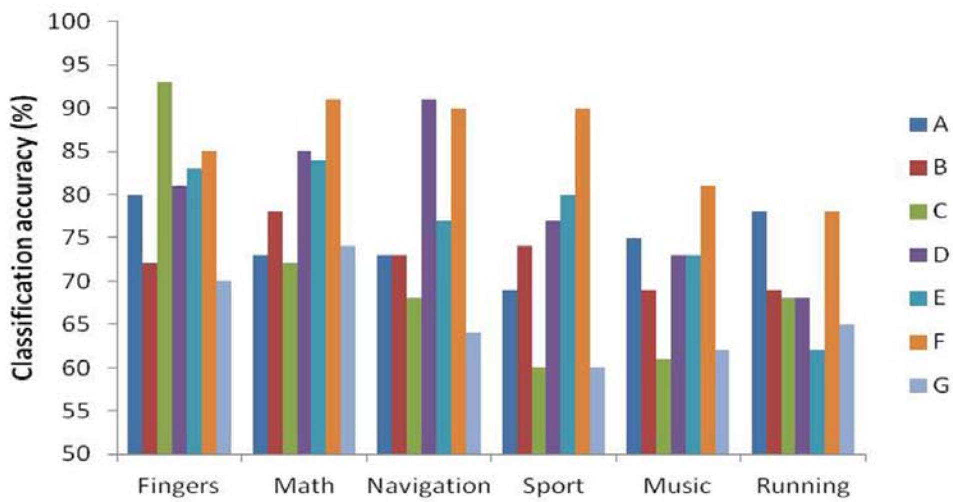

Figure 3. EEG classification accuracy for each condition vs. rest in each subject.

Subject	Math	Fingers	Navigation	Sport	Running	Music
A	3	6	2	1	5	4
B	6	3	4	5	2	1
C	5	6	3	1	4	2
D	5	4	6	3	1	2
E	6	5	3	4	1	2
F	6	3	5	4	1	2
G	6	5	3	1	4	2
Mean	5.29	4.57	3.71	2.71	2.57	2.14

Table 4. Rank of EEG classification accuracy score for each imagery condition in each subject. 6 = highest rank; 1 = lowest rank.

Friedman's ANOVA showed a significant effect of imagery condition, $\chi^2(5) = 15.41$, $p < .005$. Since Math had the highest mean rank (5.29), post hoc Wilcoxon's signed rank tests were used to compare Math to each of the other imagery conditions. While differences between Math and all other conditions except for Fingers were significant ($p < .05$) when uncorrected for multiple comparisons, after Bonferroni correction, the difference between Math and Running approached significance, z = -

2.03, $p = .11$, the difference between Math and Music approached significance, $z = -2.20$, $p = .08$, and the difference between Math and Sport remained significant, $z = -2.37$, $p < .05$.

Research Question 2: Can Robustness of Activation be Predicted from Ratings of Familiarity?

The linear regression model predicting number of active fMRI voxels from ratings of familiarity with the activity being imagined did not fit the observed data, $R^2 = .005$, $p > .5$, nor did the model predicting EEG classification accuracy from ratings of familiarity, $R^2 = .009$, $p > .5$.

The linear regression model predicting number of active fMRI voxels from ratings of imagery vividness did not fit the data, $R^2 = .041$, $p = .20$. However, the model predicting EEG classification accuracy from ratings of vividness did significantly fit the data, $R^2 = .182$, $p < .01$.

Despite the different regression outcomes, familiarity and vividness were significantly correlated, $r = .26$, $p = .05$.

Discussion

Research Question 1: Is There an Imagery Task that Provides the Most Robust Activation Regardless of Individual Differences?

In the case of fMRI, the mental arithmetic condition consistently provided the most robust activation in the vast majority of subjects and was also significantly more active than each of the other 5 imagery conditions at the group level. Navigation imagery also produced fairly robust results, rating in the top 3 in all but one subject (where it ranked 4th). Sport, finger tapping, and music imagery were more variable, while running imagery produced the least activation in all 7 subjects, in fact failing to generate any significant activation in 5 subjects.

For the classification of EEG data, the mental arithmetic condition also produced the strongest results in a majority of subjects, ranking highest in 4 subjects and in the top two in 6 out of 7 subjects, although the distinction from other imagery conditions at the group level was less pronounced than it was in the fMRI data, with only the comparison to Sport surviving correction for multiple comparisons. The classification rates for two subjects in the Sport condition failed to surpass the threshold for chance, and this was likely the reason this condition remained statistically lower than mental arithmetic. Finger tapping imagery was the second most successfully classified task, ranking in the top 3 in 5 subjects. As with the fMRI results, running and music imagery had the lowest average ranks.

In both modalities, the mental arithmetic condition was the most differentiable from rest in the majority of subjects. The present findings were supported by a series of BCI studies published while the current study was underway. Friedrich et al. (2012; 2013a; 2013b) tested several mental imagery tasks with the goal of identifying user-specific combinations of tasks that would allow for the best control of binary or 4-class EEG-based BCI. They found mental arithmetic to be among the tasks that most frequently resulted in good classification, and also among the most stable over time. The success of mental arithmetic in the present study, as well as those of Friedrich et al., may be because of the clearly defined and procedural nature of the task. For most people, even simple mental arithmetic requires focused concentration, and it recruits many higher-order cognitive functions such as working memory and executive control.

Perhaps most importantly, it has a right-or-wrong outcome by which the participant can constantly evaluate their own performance. In contrast, all of the other mental imagery conditions are open-ended in terms of the exact procedure a subject may use to generate the imagery, with no defined outcome against which a participant can monitor their performance without some sort of neurofeedback.

Regardless of the reason behind mental arithmetic's ability to produce consistent and reliable activation at the individual level, the implication is clear: it has excellent potential as a tool for the detection of awareness. If a subject is performing mental arithmetic, we can expect with a fair degree of confidence that the underlying brain activation will be observable. By no means do we suggest that this is the *only* tool necessary to assess conscious awareness – we advocate a hierarchical assessment in multiple cognitive modalities (Harrison & Connolly, 2013) – but rather that mental arithmetic should be added to existing batteries of EEG- or fMRI-based assessments, perhaps replacing some of the other commonly-used mental imagery conditions that performed less consistently in the current study.

Research Question 2: Can Robustness of Activation be Predicted from Ratings of Familiarity?

In both EEG and fMRI, ratings of familiarity failed to predict robustness of activation. The implication of this finding for the choice of mental imagery task for the assessment of awareness in disorders of consciousness is that the most suitable imagery task cannot be chosen based on a patient's personal history. With only 7 subjects, there may have been insufficient power to detect such an effect. However, ratings of vividness were able to predict EEG classification accuracy, and exhibited a trend toward prediction of fMRI activation. Meanwhile, despite a significant correlation with vividness, ratings of familiarity showed near-zero R^2 values. Unfortunately, the analysis of vividness ratings was only for validation purposes, and their predictive value is of little or no benefit for practical application to the assessment of awareness. Patients on whom mental imagery would be used to assess awareness are by definition unable to report subjective experiences. Luckily the ability to choose an imagery task based on a person's familiarity with the activity being imagined becomes less important when we consider the answer to research question 1: that mental arithmetic produced robust activation in all subjects in both EEG and fMRI, and was *the* most robust condition in a majority of subjects in both modalities. Therefore, mental arithmetic seems to be a suitable task for detection of awareness.

Research Question 3: Do fMRI and EEG Provide the Same Answers to Research Questions 1 and 2?

With the shift in focus of the field of disorders of consciousness from fMRI-based assessments to EEG-based ones, it is extremely important to be aware of the extent to which they are redundant. That is to say, can we choose to use EEG over fMRI for practical reasons (Harrison & Connolly, 2013) and be confident that we will ultimately draw the same conclusions about a patient's level of awareness? Ultimately, this question cannot be fully answered without extensive testing on patients with disorders of consciousness, but the present study provides some preliminary evidence that EEG and fMRI do give the same answers to certain questions about mental imagery. Both techniques identified mental arithmetic as the most effective imagery task for generating reliable single-subject activation, and running and music imagery as the two least effective. Neither technique's outcome appeared to be related to familiarity with the activity being imagined. In no subject do the rankings of all conditions match exactly for fMRI and EEG, however in Subject B, only the positions of lowest-ranking 2 conditions were reversed, and in over 80% of cases (34 out of 42), individual condition rankings were identical to, or within 1 position of, their rank in the other modality (Table 5).

Subject	Fingers	Math	Navigation	Sport	Music	Running
A-EEG	6	3	2	1	4	5
A-fMRI	4	6	5	2	3	1
B-EEG	3	6	4	5	1	2
B-fMRI	3	6	4	5	2	1
C-EEG	6	5	3	1	2	4
C-fMRI	5	6	4	2	3	1
D-EEG	4	5	6	3	2	1
D-fMRI	4	6	5	2	3	1
E-EEG	5	6	3	4	2	1
E-fMRI	3	6	4	5	2	1
F-EEG	3	6	5	4	2	1
F-fMRI	2	5	6	4	3	1
G-EEG	5	6	3	1	2	4
G-fMRI	4	6	3	5	2	1

Table 5. Comparison of rankings for fMRI and EEG. Exact matches are highlighted in dark grey, rankings within 1 position are highlighted in light grey.

While the correspondence between EEG and fMRI is not perfect, the degree to which the two measures agree is remarkable, considering the vastly different brain processes being measured (EEG directly measures electrical activity while fMRI measures the haemodynamic response) and the considerably divergent analyses employed (machine learning-based classification with linear and non-linear models versus classic univariate general linear model statistics). Further study with a larger sample, and validation on the target patient group are required before firm conclusions can be drawn. However, the current, preliminary results suggest that EEG can be used in place of fMRI in conjunction with a mental arithmetic paradigm as a method of detecting voluntary mental activity without loss of information.

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CHAPTER 4: GENERAL DISCUSSION

In this dissertation I have examined the application of functional magnetic resonance imaging and electroencephalographic assessments of mental imagery performance for the detection of awareness in disorders of consciousness. In Chapter 1 I presented a comprehensive review of the application of fMRI and EEG for the assessment of consciousness and cognition in disorders of consciousness. I critically evaluated the advantages and limitations of each of the two imaging modalities for investigations of disorders of consciousness. I concluded that while fMRI has contributed, and continues to contribute, greatly to our understanding of disorders of consciousness, EEG is a more practical, accessible, affordable, and safer method of assessment for these patients, and that functional imaging-based protocols should be adapted for use with EEG rather than fMRI. Chapter 2 was a technical report comparing, for the first time, two popular methods of correcting ballistocardiogram artifact in EEG data acquired simultaneously with fMRI. Simultaneous EEG/fMRI recording was the only appropriate method to address the core issue of this thesis: the concordance between EEG and fMRI on assessments of mental imagery performance. Chapter 2 was therefore an essential study to ensure the integrity of the data presented in Chapter 3. I concluded that the two methods performed approximately equally, and that with careful quality monitoring, either could be used with confidence in normal data. In Chapter 3, I investigated the concordance of fMRI and EEG measures of mental imagery performance in healthy volunteers for the purpose of guiding applications in patients with disorders of consciousness. I observed that mental arithmetic produced the most robust and reliable activation at the individual subject level. I also observed that brain activation during mental imagery was not related to the subject's familiarity with the imagined activity. Importantly, fMRI and EEG were congruent on these two findings. In the following chapter, I will discuss the significance and implications of the findings presented in this dissertation, identify limitations, and propose future research directions.

Contributions and Significance

The review presented in Chapter 1 made a significant contribution to the literature on neuroimaging studies of DOC, as reflected by its publication in an influential, high impact journal. It examined a broad field of research within a clearly defined structure of hierarchically organized cognitive functions, and synthesized findings from both EEG and fMRI – methodologies that are typically dealt with in separate literatures. Most importantly, it provided a critical evaluation of the two most frequently employed neuroimaging techniques in DOC and highlighted the difficulties inherent in performing fMRI in this patient group. The problems discussed are ubiquitous in the field, however they are rarely, if ever, mentioned in publications. It is critical to illustrate the shortcomings of a method that, on the surface, holds a great deal of promise for detecting awareness in DOC and as a result has received considerable attention in both scientific and popular media. Sensationalizing a technique without an accompanying discussion of its pitfalls may lead to an intensification of research efforts on an impractical technique, rather than focusing them on finding feasible alternatives. After all, the ultimate goal of neuroimaging research on disorders of consciousness is to be able to identify all cases in which an inaccurate diagnosis of VS has been made. But if research efforts focus on a technique that can only be applied to a small subset of the patients in question, the issue has not been far advanced and the majority of misdiagnoses will remain undetected. The arguments presented in Chapter 1 illustrate that the theoretical potential of a technique can be cancelled out by the practical considerations necessary to translate research into clinical practice, an issue that is far too often ignored. Chapter 1 therefore provides a solid, practical argument for a transition from the development of fMRI-based assessments in DOC to a focus on EEG-based methods.

Chapter 2 provided, for the first time, an evaluation of the two most widely used BCG correction algorithms as they are implemented in two popular EEG processing software tools. Much research in the signal processing field has focused on the development of novel BCG correction algorithms, but few of these have been made available to researchers who are recording simultaneous EEG and fMRI for purposes other than the development of artifact correction algorithms. No previous studies have directly compared the two algorithms discussed in Chapter 2, and as such it provides a practical and concrete guide for the selection of a BCG correction algorithm in the case that novel methods of artifact correction are not a primary goal of a study. Certainly, much time and many resources would have been saved in the case of the current dissertation had this study been previously available. Importantly, the study also served as a quality assurance step in the analysis of the data for Chapter 3. The validity of EEG data acquired simultaneously with fMRI is heavily contingent upon proper correction of artifact, and Chapter 2 verified that the algorithms applied were effective.

Chapter 3 made several significant contributions. First was the finding that mental arithmetic elicits the most robust and reliable activation at the individual subject level. This has a clear implication for the detection of awareness in DOC. It provides a simple, straightforward paradigm that is highly likely to generate detectable activation in DOC patients if they are, in fact, covertly aware and able to perform the task. Previous studies that have used tennis, swimming, navigation, or hand/foot imagery (e.g., Bardin et al., 2011; Cruse et al., 2011; Goldfine et al., 2011; Monti et al., 2010) – conditions which produced less robust activation in the current study – may have been able to identify further cases of covert awareness had they employed the mental arithmetic task instead of, or in addition to, the other tasks. The second important finding from Chapter 2 was that robustness of activation cannot be predicted from the subject's familiarity with the imagined activity. This also has important implications for the selection of imagery tasks for detecting awareness. If the hypothesized relationship between familiarity and brain activation had held, the imagery task most likely to generate detectable activation could have been selected based on a patient's personal history, interests, and abilities. However, the finding that mental arithmetic was the most robust in nearly every subject removes the need to predict activation from familiarity, and so the lack of relationship between the two measures becomes irrelevant for the selection of an appropriate imagery task. Mental arithmetic can be used with confidence that if the subject is performing the task, the activation will be detectable. The third significant contribution from Chapter 3 is the confirmation that EEG and fMRI provide the same information about mental imagery performance. This is critical to the field of disorders of consciousness at this particular juncture. Researchers are adopting EEG instead of fMRI as the method of choice for detecting awareness in DOC. However there has been no verification of the convergence of the two methods in terms of the conclusions that would be drawn about an individual patient's state of consciousness. This study supported the shift from fMRI to EEG by showing that the two methods converge on several important variables. EEG can therefore be used to assess mental imagery performance with confidence that the information gained will be redundant with fMRI. Of course, validation of this finding in patients with DOC is necessary, and EEG of mental imagery shouldn't be used in isolation, but rather as a part of a hierarchical assessment battery. In the case of a negative finding, fMRI would provide a useful alternative method to verify the finding, when it is possible in a given patient. A new diagnostic category, functional locked-in syndrome, has been proposed for those patients who receive a diagnosis of VS based on traditional bedside assessments, but who show evidence of awareness when brain-based measures such as fMRI or EEG are employed (Bruno et al., 2011). Taken together, the findings from Chapter 3 suggest that a machine-learning based classification approach using EEG recorded during mental arithmetic and rest should provide a reliable tool to detect awareness in DOC and thus a potential diagnostic marker for this new category.

Limitations

The studies presented in this dissertation have several limitations that must be considered along with their contributions. The first of these is the small sample sizes employed. In Chapter 3 the reduced sample size was due to the discarding of half of the collected data for technical reasons that could not be diagnosed at the time of writing. The fMRI data exhibited a pattern such that the first seven subjects showed appropriate activation during the imagery tasks with expected amounts of within- and between-subject variability, but the last seven subjects showed virtually no activation after the conjunction analysis with individual runs exhibiting lack of activation or suspicious noise patterns. This overall pattern was deemed too coincidental to be due purely to subject variables, and statistical analysis confirmed that the two halves of the data belonged to different distributions. However, no scanner specific variables could be identified to coincide with the pattern in the data, including SNR and significant changes to scanner hardware that occurred between the testing of the first seven subjects and the second set of seven. It was decided that the data were not of sufficient quality to be included in the analysis. The majority of analyses in both studies took place at the individual subject level, so large groups were not required for statistical power in those cases. However, a larger number of subjects would give a more accurate picture of individual variability and allow for broader generalization of the findings in Chapters 1 and 2. Additionally, in Chapter 3, confidence in the results of the ANOVAs for differences between imagery conditions and the regressions of activation onto familiarity would have benefitted from the additional statistical power afforded by a larger sample. Small sample sizes were also an issue in Chapter 1. A large number of the studies reviewed reported findings from either a single patient, or a very small group of patients. The problem of small samples is inherent in research on DOC as there are few centres where these patients appear in large numbers, so caution must be used when interpreting and generalizing findings.

Chapter 3 is also limited by the exclusive use of healthy volunteers. Ideally, the test groups would have been comprised of a group of patients diagnosed with DOC, a group of patients with locked-in syndrome to serve as conscious, brain-injured controls, as well as the healthy volunteers. However, for the host of reasons discussed in chapters 1-3, it was not possible to perform the simultaneous EEG/fMRI recordings on patients. Follow-up studies on DOC patients are imperative before the findings can be translated for clinical use (see Future Directions, below).

An important limitation of the use of mental arithmetic for diagnostic purposes is the considerable cognitive demand it places on the subject, which may be too high for some brain-injured patients. The intensive concentration and coordinated mental function required to successfully perform the task may be unachievable or unsustainable for a severely brain-injured patient despite the presence of conscious awareness. If any one of the component cognitive functions required to perform mental imagery, such as executive function, language (to comprehend instructions and trial cues), or working memory is impaired, the patient may not be able to generate brain responses reflective of awareness. This applies equally to all imagery-based paradigms. Therefore, mental imagery of any kind can never be used in isolation for diagnostic purposes. It must form part of a hierarchical and multi-modal battery of tests to assess all levels of cognitive function. It should also be noted that it may be valuable to use more than one form of imagery when possible. A patient's specific injury may prevent performance of a particular type of imagery (e.g., a stroke affecting the motor cortex may impair motor imagery) and so a second imagery task in a different cognitive modality may increase the chance of detecting awareness.

Direct comparison of the results of the imagery study in Chapter 3 to previously published work may be limited by some of the modifications made to the paradigm. The 'Running' condition has not previously been employed, but was meant to be comparable to the tennis and swimming imagery conditions employed in other studies (e.g., Boly et al., 2007; Monti et al., 2010; Owen et al., 2006), in that it is a full-body physical activity. Running was chosen rather than tennis or swimming because an activity was desired with which every subject would certainly be familiar. In Canada, tennis is not a very widely played sport, and while swimming is certainly more familiar, it is still an activity with which some subjects may not have experience. Running, on other hand, is something that all healthy volunteers will have had some experience. Ultimately, the hypothesized relationship between familiarity and activation was not supported, but it is possible that there are still inherent differences in the activation generated by running imagery compared to swimming or tennis imagery. Also, the finger tapping imagery condition, which was meant to be analogous to the hand movement imagery in other studies (Curran et al., 2004; Neuper et al., 2006; Pfurtscheller & Neuper, 1997; Wolpaw et al., 2002), used slightly different instructions (imagine pressing a button with each finger in succession) than other studies (e.g., imagine squeezing and relaxing hand). These differences should be taken into account as possible sources of variability when comparing the present results to other studies.

A possible limitation of the comparison between the fMRI and EEG results in Chapter 3 is the different analysis methods used in each case. For the fMRI data, a traditional, univariate GLM approach was applied to model the changes in BOLD for each imagery condition versus rest. For the EEG data, on the other hand, a complex, multivariate, machine learning procedure was applied to find a structure in the data which allowed maximal separation between each imagery condition and rest. A similar, machine learning-based approach could be applied to the fMRI data. A multivariate pattern analysis (MVPA) would take into account spatial patterns of activation in addition to voxel-wise increases or decreases in BOLD in the same way that the EEG machine learning analysis considers both coherence between brain regions as well as PSD. MVPA would potentially provide additional evidence of mental imagery performance that is not revealed with traditional univariate techniques (Bardin, Schiff,

& Voss, 2012), and could add a layer of information to the fMRI findings presented in Chapter 3 as well as their relationship to the EEG outcomes.

Future Directions

The findings presented in this dissertation open several avenues for future research. The most immediate of these would be to verify the generalizability of the findings from Chapter 3 by testing mental arithmetic against standard imagery tasks such as tennis/swimming, navigation, and hand/foot imagery in patients with DOC. Based on the findings from Chapter 3, performance of mental arithmetic should result in the identification of a greater number of covertly aware patients than the other paradigms. The evidence from Chapter 3 suggesting concordance between EEG and fMRI would also support the hypothesis that EEG and fMRI would identify the same individuals as being covertly aware. Ideally, the recordings would be done simultaneously, but again, this is not feasible in DOC patients and so the recordings would likely have to be done separately. Separate testing sessions would introduce an additional set of session-dependent variables (e.g., arousal, attention, learning, positioning) whose influence on the concordance between EEG and fMRI would have to be carefully considered.

The current findings also support recent investigations of mental arithmetic as a control mechanism for brain-computer interfaces (BCI; Friedrich, Neuper, & Scherer, 2013; Friedrich, Scherer, & Neuper, 2012, 2013). The vast majority of studies of mental imagery for BCI control use hand or foot motor imagery. While this type of imagery may be more intuitive and directly translatable to the desired outcome (e.g., left hand imagery to move a cursor to the left, and right hand imagery to move it to the right), the success rates of these types of BCIs are far from perfect, particularly for end users with disabilities (Leeb et al., 2013). Mental arithmetic may provide a useful control mechanism that would provide increased success for some users and the recent studies from Friedrich and colleagues cited above provide preliminary support for this claim. The finding that activation related to mental arithmetic was easier to detect than other imagery conditions suggests that there is some aspect of the task that facilitates engagement and sustained concentration. It was proposed in the discussion of Chapter 3 that this may be due to the well-defined nature of the task and the right-or-wrong outcome against which the participant can evaluate their ongoing performance, in contrast to the dynamic and non-specific nature of the other imagery tasks. By this logic, other well-defined mental "work" tasks may also produce robust and reliable activation. Future studies could investigate the relative performance of tasks like word generation, mental rotation, subvocal recitation of, for example, reverse alphabet, as additional potentially useful tasks for the detection of awareness. BCI researchers have recently investigated a number of such tasks in addition to mental arithmetic (Friedrich et al., 2013a; Friedrich et al., 2012; Friedrich et al., 2011; Friedrich et al., 2013b) and have found their EEG signatures to be distinctive from other classes of mental imagery, making them useful as potential control mechanisms for BCI, and thus also likely candidates for detection of awareness. A necessary element of studies of these tasks for the detection of awareness, that has been absent from DOC research to date, is the estimation of sensitivity and specificity. There is frequently a dissociation between diagnoses and imaging findings, in both directions – patients diagnosed as VS/UWS who exhibit imaging evidence of awareness, but also patients who can communicate at bedside who do not show corresponding imaging evidence of awareness (Bardin et al., 2011; Coleman et al., 2009; Faugeras et al., 2011; Faugeras et al., 2012).

A useful follow-up study to the evaluation of BCG correction algorithms in Chapter 2 would be a similar comparison of the same algorithms on data of suboptimal quality. EEG data from many patient populations is prone to artifact from motion, EMG, excessive eye movement such as eye rolling or nystagmus, and slow potentials due to sweating or oily scalp, all of which are absent or easy to control in healthy subjects. The ability of each algorithm to deal with noise from these sources is of critical importance for any simultaneous EEG/fMRI studies on patient populations.

Conclusions

In this dissertation I have explored the use of fMRI and EEG to detect performance of various mental imagery tasks within the framework of the assessment of awareness in disorders of consciousness. I have also provided an evaluation of the effectiveness of artifact removal methods for simultaneous EEG/fMRI recordings. I have demonstrated that mental arithmetic produces the most robust and consistent activation compared to navigation imagery, music imagery, physical activity imagery, finger movement imagery, and running imagery, at the individual level in a strong majority of subjects. Furthermore, I have demonstrated clear agreement between fMRI and EEG on these measures. Taken together, these findings provide a solid foundation for the further development of EEG-based assessments for disorders of consciousness.

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