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Decoding Mental States after Severe Brain Injury

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Abstract

Some patients with disorders of consciousness retain sensory and cognitive abilities that are not apparent from their outward behaviour. It is crucial to identify and characterise these covert abilities for diagnosis, prognosis, and medical ethics. This thesis uses neuroimaging techniques to investigate cognitive preservation and awareness in patients who are behaviourally non-responsive due to acquired brain injuries. In the first chapter, a large sample of healthy volunteers, including experienced athletes and musicians, imagined actions of varying complexity and familiarity. Motor imagery involving certain complex, familiar actions correlated with a more robust sensorimotor rhythm. In the second chapter, several patients with disorders of consciousness participated in multiple experiments based on neural responses to mental imagery, including one task featuring complex, familiar imagined actions. Although the patients did not generate enhanced sensorimotor rhythms for the complex, familiar motor imagery, the detection of covert cognition was more sensitive owing to the multi-modal nature of the assessment. In the final empirical chapter, a sample of healthy volunteers and a heterogeneous cohort of patients with disorders of consciousness completed a novel oddball task based on tactile stimulation. Critically, this task delineated an attentional hierarchy in the patient sample, and patients with the ability to follow commands were differentiated from those unable to do so by event-related potential evidence of attentional orienting. Due to the heterogeneity of aetiology and pathology in the disorders of consciousness, these patients vary in their suitability for neuroimaging, the preservation of neural structures, and the cognitive resources available to them. Assessments of several perceptual and cognitive abilities supported by spatially-distinct brain regions and indexed by multiple neural signatures are therefore required to accurately characterise a patient’s abilities and probable subjective experience.

Keywords

Mental imagery, attention, sensorimotor rhythm, event-related potential, awareness, disorders of consciousness.

Co-Authorship Statement

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As author of this thesis and first author of the published papers associated with Chapters 2, 3, and 4, Raechelle M. Gibson was the primary contributor to all stages of the described investigations including: experimental design; data collection, analysis, and interpretation; and writing. Drs. Owen and Cruse provided expert advice and supervision for all stages of the work. Drs. Owen and Cruse also conceived of the early assessments of covert command following cited throughout the thesis. Dr. Chennu provided expertise and feedback during the writing of the published papers associated with Chapters 2 and 4. Dr. Fernández-Espejo acquired and analysed the functional magnetic resonance imaging data presented in Chapter 3. Drs. Fernández-Espejo and Naci acquired and analysed the functional magnetic resonance imaging data presented in Chapter 4. Drs. Naci and Owen conceived of the functional magnetic resonance imaging-based selective auditory attention paradigm included and cited in Chapter 4. Dr. Gonzalez-Lara contributed to the clinical behavioural assessments of the patients discussed in Chapters 3 and 4 and offered useful feedback on the manuscripts for the same two chapters. Finally, Drs. Kwan and Lee (clinical radiologists) contributed the clinical assessments of the anatomical brain images from the patients discussed in Chapter 3.

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List of Abbreviations

Abbreviations that only appear in a table or figure are defined in the corresponding table notes or figure caption and are not included here.

EEG: electroencephalography

[f]MRI: [functional] magnetic resonance imaging

***M*:** mean

***SD*:** standard deviation

***SE*:** standard error

Chapter 1

1 General Introduction

1.1 Disorders of consciousness

Following a severe head injury, a person may enter a non-responsive state referred to as coma. Patients in a comatose state often require life-sustaining therapies and do not respond to external stimulation (Plum & Posner, 1972). Upon emergence from coma, some patients resume alternating periods of eye-opening and quiescence that resemble healthy sleep-wake cycles, alongside absent or inconsistent behavioural responsiveness (Bernat, 2006; Fernández-Espejo & Owen, 2013; Giacino, Fins, Laureys, & Schiff, 2014). Patients who do not exhibit voluntary responses to external stimulation are diagnosed as being in a Vegetative State (Bernat, 2006; Jennett, 2002). Diagnostic criteria for the Vegetative State were initially described in 1972 (Jennett & Plum, 1972). Several international task forces have revisited these criteria since then (*e.g.*, Andrews, 1996; Multi-Society Task Force on PVS, 1994a; Royal College of Physicians Working Group, 1996, 2003). Across all iterations, however, there is consensus that patients in a Vegetative State lack awareness. To more accurately and sensitively describe the Vegetative State, it was recently proposed that this disorder be renamed Unresponsive Wakefulness Syndrome (Laureys *et al.*, 2010). In 2002, formal diagnostic criteria for the Minimally Conscious State were proposed to describe patients who generate variable, but reproducible, voluntary responses to external stimulation (Giacino *et al.*, 2002). Patients in a Minimally Conscious State possess awareness, and the ability to follow verbal commands may be indicated by a diagnostic qualifier of 'Plus' if present (Minimally Conscious State *Plus*), or 'Minus' if absent (Minimally Conscious State *Minus*; Bruno *et al.*, 2012; Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011). Emergence from a Minimally Conscious State is indicated when a patient demonstrates functional, accurate communication or functional object use (Giacino *et al.*, 2002). Together with coma and brain death, these altered states of awareness following brain injury comprise the disorders of consciousness (Table 1).

Table 1. Overview of the disorders of consciousness.

Diagnosis	**Description**	**Characteristic Behaviour**	**Command Following and Communication**
Brain death	Loss of all brainstem reflexes and absence of breathing (continuing apnoea)	None	None
Coma	Closed eyes without responsiveness to stimulation for no more than about four weeks	None, although some patients may exhibit reflexive responses to pain	None
Vegetative State/ Unresponsive Wakefulness Syndrome Non-behavioural Minimally Conscious State	Periods of eye-opening without reproducible, voluntary responses to stimulation Sometimes denoted as a non-behavioural Minimally Conscious State when command following is demonstrated in a neuroimaging-based assessment	None, or reflexive behaviour, including any of: *Startle responses (auditory or visual);* *abnormal posturing;* *withdrawal (motor);* *reflexive oral movements;* and/or *localization to sound*	None Patients in a non-behavioural Minimally Conscious State demonstrate command following in a neuroimaging-based assessment
Minimally Conscious State (*Plus* or *Minus*)	Periods of eye-opening with reflexive and voluntary behaviour Sometimes denoted as Minimally Conscious State *Plus* when behavioural command following is present, or Minimally Conscious State *Minus* when behavioural command following is absent	Reproducible reflexive and voluntary behaviour, including at least one of: *Visual fixation or pursuit;* *object localization, recognition, or manipulation;* *orientation to noxious stimulation;* or *automatic motor responses*	Minimally Conscious State *Minus* patients demonstrate none Minimally Conscious State *Plus* patients demonstrate at least one of: *Reproducible or consistent movement to command;* *intelligible verbalization;* or *non-functional, intentional communication*
Emergence from a Minimally Conscious State	Periods of eye-opening with reflexive and sophisticated voluntary behaviour	Reproducible reflexive and voluntary behaviour, including at least one of: *Accurate functional communication*; and/or *functional object use*	At least one of: *Accurate, functional communication;* or *functional object use*

Notes. All behavioural criteria are taken from the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005).

Disorders of consciousness are often caused by traumatic brain injuries (Bernat, 2006; Pisa, Biasutti, Drigo, & Barbone, 2014). A patient may also enter these states following a non-traumatic brain injury, which commonly occurs from hypoxia secondary to cardiac arrest or stroke (Bernat, 2006; Tresch, Sims, Duthie, Goldstein, & Lane, 1991). Additionally, an adult patient with a neurodegenerative disease, such as Parkinson's or Huntington's, may progress to a Minimally Conscious State in the final stages of his or her illness (Walshe & Leonard, 1985). Regarding pathology, traumatic cases of disorders of consciousness usually include diffuse axonal injury in white matter alongside other neuronal damage from injuries such as cortical contusions, increased intracranial pressure, and cerebral haemorrhages (Adams, Graham, & Jennett, 2000). In non-traumatic cases of disorders of consciousness involving hypoxia, extensive damage to cortical and thalamic grey matter is common (Dougherty, Rawlinson, Levy, & Plum, 1981). Total grey matter volume, however, does not necessarily differentiate between the Vegetative State and Minimally Conscious State (Di Perri *et al.*, 2016). The Vegetative State and Minimally Conscious State differ such that the Vegetative State usually corresponds with more severe pathological changes than the Minimally Conscious State (Bernat, 2006; Jennett, Adams, Murray, & Graham, 2001). Brainstem and hypothalamic structures are typically preserved in all patients with disorders of consciousness (Kinney & Samuels, 1994). In this thesis, all patient cohorts comprise convenience samples of adults with acquired brain injuries of traumatic, non-traumatic, or mixed (*i.e.*, both traumatic and non-traumatic) aetiology. Although details are provided concerning the aetiology and pathology of each patient's brain injuries, a group-level examination of these factors is not included because the convenience samples are small and highly heterogeneous.

Disorders of consciousness are usually denoted with an acute or chronic time course. Some patients temporarily exhibit a Vegetative State or Minimally Conscious State as they recover from a head injury, while other patients remain in these states until the end of their lives. Assuming the same diagnosis, a patient with a non-traumatic brain injury is less likely to regain awareness than a patient with a traumatic brain injury (Multi-Society Task Force on PVS, 1994a, 1994b). Additionally, a patient's likelihood of recovering awareness decreases the longer the patient persists in the same conscious state. For example, the probability that an adult patient in a Vegetative State recovers awareness is less than 1% after 3 months following a non-traumatic brain injury and after 1 year following a traumatic brain injury (Multi-Society Task Force on PVS, 1994a, 1994b). For patients in a Minimally Conscious State for less than 1 month post-injury, up to 50% will return to an independent life after 1 year (Giacino, 2004). For patients who persist in a Minimally Conscious State for 1 month or longer, however, outcomes considerably vary after 2 to 5 years; some patients exhibit mild disabilities with total functional independence, while other patients remain severely disabled and completely dependent on others (Lammi, Smith, Tate, & Taylor, 2005). Notably, there are several reports of seemingly spontaneous recoveries of awareness beyond these timelines for patients with disorders of consciousness (*e.g.*, Arts, van Dongen, van Hof-van Duin, & Lammens, 1985; Rosenberg, Johnson, & Brenner, 1977; Wilson, Gracey, & Bainbridge, 2001). Additionally, there a few reports of patients who exhibited at least a partial recovery of awareness after treatment with targeted therapy, including deep brain stimulation and various drugs (*e.g.*, Clauss & Nel, 2006; Georgiopoulos *et al.*, 2010; Sarà *et al.*, 2007; Tsubokawa *et al.*, 1990). Nevertheless, there is currently no evidence-based, curative treatment available for disorders of consciousness, and patients with chronic disorders of consciousness are very unlikely to recover functional independence.

It is difficult to estimate the life expectancy for patients with disorders of consciousness. This difficulty arises in part due to the self-fulfilling prophecy that patients with poor or uncertain prognosis may be provided with less life-sustaining therapy in the acute phase of treatment and less active medical management in the chronic phase (Becker *et al.*, 2001; Bernat, 2006; Weimer, Nowacki, & Frontera, 2016). In terms of acute treatment, there currently are prognostic indicators of only poor recovery available for patients in a coma or acute Vegetative State (Bates, 2001; Teasdale *et al.*, 2014; Zandbergen, de Haan, Stoutenbeek, Koelman, & Hijdra, 1998). Likewise, there are no reliable prognostic indicators for patients in an acute Minimally Conscious State (Giacino & Kalmar, 2007; Lammi *et al.*, 2005). For patients who lack indicators of poor recovery in this critical acute treatment phase, possible outcomes include death, chronic disorders of consciousness, various levels of disability, and full functional recovery (Teasdale *et al.*, 2014; Zandbergen *et al.*, 1998). Understandably, this uncertainty complicates the decision to continue or withdraw life-sustaining therapies. During the chronic treatment phase, medical comorbidities are common and often arise shortly after the patient is transferred to a rehabilitation unit for continuing care (Whyte *et al.*, 2013). Examples of common medical complications include urinary tract infections and pneumonia, and patients with chronic disorders of consciousness may die from undetected or insufficiently managed infections. Nevertheless, medical complications become less frequent with time, and active management typically reduces reoccurrence and severity (Whyte *et al.*, 2013). In fact, patients who sustain injuries early in adulthood with appropriate management of comorbidities can survive for years with artificial nutrition and hydration (Bernat, 2006). All patients described in this thesis exhibited chronic disorders of consciousness, and several of the patients presented with the same conscious state for a decade and longer.

Prevalence data concerning disorders of consciousness are difficult to obtain due to variability in international diagnostic criteria and few large-scale, multi-centred investigations. A recent epidemiological review of primarily European centres obtained prevalence estimates of 0.2 to 3.4 cases per 100,000 inhabitants for patients in a Vegetative State and 1.5 per 100,000 inhabitants for patients in a Minimally Conscious State (Pisa *et al.*, 2014). Traumatic aetiology accounted for 21.9% to 53.8% of all cases (Pisa *et al.*, 2014). An older report estimated the prevalence of the Vegetative State in the United States of America and Europe at 1.4 to 6.7 per 100,000 inhabitants from 1 month post-injury, and this estimate decreased to 0.5 to 2.5 per 100,000 from 6 months post-injury (Jennett, 2002). Unfortunately, there were no epidemiological studies of disorders of consciousness in Canada available at the time of writing. Nevertheless, brain injury is common in Canada; for example, about 15,300 Canadians were hospitalized due to traumatic brain injuries in 2003, accounting for about 8% of all admissions for trauma that year (Canadian Institute for Health Information, 2006). Additionally, the average direct medical cost of the first year post-injury in the same period was $31,000 per patient for those with traumatic injuries and $38,000 per patient for those with non-traumatic injuries (Chen *et al.*, 2012). Although true disorders of consciousness are relatively uncommon, these disorders present challenging medical and scientific questions that are subject to investigation from many special interest groups around the world (Gosseries, Zasler, & Laureys, 2014).

Standards of care for patients with chronic disorders of consciousness are similar worldwide. Recommended care includes: nutrition via gastrointestinal tube feeding; range of motion exercises to counteract muscular contractures (spasticity); and tracheostomy with suctioning and other pulmonary hygiene interventions for airway protection (Sandel, 1996). This complex continuing care can be provided in a patient's home or in an assisted living facility. In Canada and many other nations, substitute decision makers provide consent pertaining to medical care and other aspects of living for patients who lack the capacity to do so themselves (Rocker & Dunbar, 2000). The substitute decision maker is meant to: (1) express the choices the patient would make if he or she were able to do so; and (2) act in the patient's best interest if the patient's likely decision is unknown (Rocker & Dunbar, 2000). Substitute decision makers provided informed, written consent for all patients who participated in the research reported in this thesis in line with the guiding principles of the local Canadian ethics committees.

Given that a full functional recovery is uncommon and unlikely for many patients with chronic disorders of consciousness, substitute decision makers and others involved in the patient's medical care may consider assisted dying or the withdrawal of life-sustaining measures for the patient (Andrews, 2004; Cranford, 1984; Laureys, 2005a). Opinions on assisted dying and the legalities concerning the different forms of this practice vary (*e.g.*, Schüklenk *et al.*, 2011; Smedira *et al.*, 1990; Solomon *et al.*, 1993). To further complicate matters, the withdrawal of life-sustaining treatments for most patients with chronic disorders of consciousness necessitates the cessation of nutrition and hydration because these patients can usually breathe without assistance. Although not uncommon in some areas of medicine and in natural death by component patients, this practice is understandably controversial (Ganzini *et al.*, 2003; Meilaender, 1984; Tsai, 2011). There have been a few cases involving patients with disorders of consciousness in the United States of America and Canada where referrals have been made to court to address disagreements about medical decision-making (*e.g.*, Downar, Sibbald, Bailey, & Kavanagh, 2014; Quill, 2005; Rich, 2013). Although there are several moral, legal, and ethical problems surrounding the withdrawal of life sustaining therapies for patients with disorders of consciousness in particular (see [Jennett, 2002] for a detailed discussion), the paramount consideration is that the wishes of the patient are respected (Gillon, 1998). If the patient's wishes are unclear, medical societies and governing bodies worldwide recommend continued treatment even when recovery is unlikely (American Academy of Neurology, 1989; British Medical Association, 2001; Rocker & Dunbar, 2000).

1.2 Differential diagnosis and restoration of communication

To differentially diagnose disorders of consciousness—*i.e.*, to determine whether a patient is in a Vegetative State or a Minimally Conscious State, a clinician must carefully assess the patient's responsiveness to stimulation to infer whether the patient is conscious. Repeated assessments are necessary to distinguish between random or reflexive responses and reliable, voluntary responses. Given the difficulty of this clinical determination, several specialized instruments have been developed to facilitate the differential diagnosis of the Vegetative State and Minimally Conscious State in particular (Shiel, Gelling, Wilson, Coleman, & Pickard, 2004). The preferred neuropsychological instrument for this purpose is the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005). This instrument has been validated in patients with disorders of consciousness (Giacino, Kalmar, & Whyte, 2004) and found to most sensitively distinguish between the Vegetative State and Minimally Conscious State as compared to alternative instruments (Seel *et al.*, 2010). The Coma Recovery Scale is also preferred to other behavioural assessments for disorders of consciousness because it requires less training and can be more readily adopted by clinicians who cannot access specialized neurorehabilitation units (Bernat, 2006; *cf.* Gill-Thwaites & Munday, 1999; Pape, Heinemann, Kelly, Hurder, & Lundgren, 2005). If different diagnoses are obtained across time, it is conventional to report a patient's diagnosis according to that patient's most sophisticated performance. In this thesis, each patient's conscious state was determined using his or her best performance on the Coma Recovery Scale. Differential diagnoses across time are discussed when present, and all assessments were validated to ensure that no impossible or improbable combinations of Coma Recovery Scale scores were obtained (Chatelle *et al.*, 2016).

Administration of the Coma Recovery Scale entails a neuropsychological assessment across several sensory domains categorised into six subscales (Kalmar & Giacino, 2005). As shown in Table 2, each test item probes the patient's ability to exhibit behavioural responses following direct stimulation or verbal command. Within each subscale, involuntary and reflexive behavioural responses are evaluated first; these responses only require one or two trials to assess. If these involuntary responses are intact, increasingly complex, voluntary behavioural responses are then probed. The patient must demonstrate each voluntary response three or four times in an assessment for that response to be scored as reliable and intact. Assessment of each subscale ends when the patient does not reliably demonstrate a probed response, or when the patient reliably demonstrates all behavioural responses for that subscale (and thus obtains the highest possible score). For example, the first test item on the oromotor/verbal function subscale is oral reflexive movement. An intact response constitutes immediate movements of the tongue or jaw, such as clamping or chewing, after a tongue blade is introduced into the patient's mouth. Only one trial is needed to probe this response; an intact response corresponds with a score of 1, while a lack of response corresponds with a score of 0. Additionally, the highest possible score (3) on the oromotor/verbal function subscale is intelligible verbalization. This behavioural response would only be probed if the patient first reliably demonstrated oral reflexive movement (a score of 1) and vocalization/oral movement (a score of 2). To reliably demonstrate intelligible verbalization, the patient must generate consonant-vowel-consonant sounds for at least two different words in response to prompts such as "What is your name?" and "How many fingers am I holding up right now?". Notably, reliable intelligible verbalization is a voluntary response indicative of a Minimally Conscious State (Kalmar & Giacino, 2005).

Table 2. Summary of the JFK Coma-Recovery Scale-Revised subscales.

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Auditory Function	**Oromotor/Verbal Function**
4 – Consistent Movement to Command*	3 – Intelligible Verbalization*
3 – Reproducible Movement to Command*	2 – Vocalization/Oral Movement
2 – Localization to Sound	1 – Oral Reflexive Movement
1 – Auditory Startle	0 – None
0 – None	
Visual Function	**Communication**
5 – Object Recognition*	2 – Functional: Accurate†
4 – Object Localization: Reaching*	1 – Non-Functional: Intentional*
3 – Visual Pursuit*	0 – None
2 – Fixation*, [a]	
1 – Visual Startle	
0 – None	
Motor Function	**Arousal**
6 – Functional Object Use†	3 – Attention
5 – Automatic Motor Response*	2 – Eye Opening without Stimulation
4 – Object Manipulation*	1 – Eye Opening with Stimulation
3 – Localization to Noxious Stimulation*	0 – Unarousable
2 – Flexion Withdrawal	
1 – Abnormal Posturing	
0 – None/Flaccid	

Notes. *Denotes Minimally Conscious State; †Denotes emergence from a Minimally Conscious State.

[a]Sustained visual fixation does not necessarily reflect higher order cortical brain function in patients with disorders of consciousness and non-traumatic aetiology (Bruno *et al.*, 2010).

A critical diagnostic marker in disorders of consciousness is whether a patient can follow commands. Patients who follow commands in a bedside behavioural examination are attributed with at least minimal consciousness, while patients who do not are regarded as ‘unaware’, *i.e.*, diagnosed as being in a Vegetative State (Andrews, 1996; Jennett & Plum, 1972; Multi-Society Task Force on PVS, 1994a; Royal College of Physicians Working Group, 1996, 2003). Unfortunately, a patient’s ability to outwardly respond may be compromised for many reasons, such as cognitive impairments due to brain injury or damage to the peripheral motor system (Giacino *et al.*, 2014; Whyte *et al.*, 2013). Accordingly, a patient could retain awareness and be inaccurately diagnosed as being in a Vegetative State because he or she does not overtly respond during a behavioural assessment (Gosseries, Di, Laureys, & Boly, 2014; Owen, 2013). The rate of misdiagnosis of a patient’s conscious state is high; as many as 43% of patients diagnosed as being in a Vegetative State have been found to exhibit signs of awareness after careful follow-up testing in a neurorehabilitation unit (Andrews, Murphy, Munday, & Littlewood, 1996; Candelieri, Cortese, Dolce, Riganello, & Sannita, 2011; Childs, Mercer, & Childs, 1993; Schnakers *et al.*, 2009). Moreover, the consequences of such misdiagnoses are severe. For example, false negatives—*i.e.*, inferring that a patient does not possess awareness when he or she does—could lead to the premature withdrawal of life sustaining therapies and inadequate medical management of the patient (Jox, Bernat, Laureys, & Racine, 2012; Peterson, Cruse, Naci, Weijer, & Owen, 2015). Similarly, false positives—*i.e.*, inferring that a patient possesses awareness when he or she does not—could lead to a missed opportunity to withdraw life sustaining therapies and needless financial and emotional suffering for the patient’s family (Jox *et al.*, 2012; Peterson *et al.*, 2015). Due in large part to these legal, ethical, and moral challenges, the detection of awareness in patients with disorders of consciousness has been the subject of increasing research for about twenty years (Gosseries, Zasler, *et al.*, 2014; Jennett, 2002; Peterson *et al.*, 2013; Racine & Illes, 2007).

To address the challenge of accurate diagnosis in disorders of consciousness, researchers and clinicians have used neurophysiological markers of sensory and cognitive function to complement behavioural assessments. Several neural markers have been identified that can facilitate the differential diagnoses of disorders of consciousness. For instance, patients in a Vegetative State tend to have more metabolic dysfunction in frontoparietal networks than patients in a Minimally Conscious State (Cavinato *et al.*, 2015; Demertzi, Soddu, & Laureys, 2013; Thibaut *et al.*, 2012). At rest or during passive stimulation, patients in a Minimally Conscious State have increased cerebral metabolism and functional connectivity as compared to patients in a Vegetative State (Kotchoubey *et al.*, 2013; Laureys, Faymonville, Degueldre, *et al.*, 2000; Laureys, Owen, & Schiff, 2004). Moreover, the structural integrity of thalamocortical pathways is higher in patients who demonstrate more behavioural signs of awareness (Fernández-Espejo *et al.*, 2012; Laureys, Faymonville, Luxen, *et al.*, 2000; Schiff, 2008). While these passive approaches have revealed valuable information about brain function and metabolism in patients with disorders of consciousness, researchers have also used neuroimaging techniques to determine whether a patient who is outwardly non-responsive can volitionally modulate his or her brain activity—and in so doing, provide evidence of his or her ability to follow commands.

Neuroimaging techniques have been applied to determine whether patients with disorders of consciousness can modulate their brain activity in response to commands. Of these techniques, one of the most widely adopted involves asking a patient to engage in mental imagery during either a functional magnetic resonance imaging (fMRI) scan (Bardin *et al.*, 2011; Boly *et al.*, 2007; Fernández-Espejo & Owen, 2013; Gibson, Fernández-Espejo, *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006; Stender *et al.*, 2014) or a recording session with electroencephalography (EEG; Coyle, Stow, McCreadie, McElligott, & Carroll, 2015; Cruse *et al.*, 2011; Gibson, Fernández-Espejo, *et al.*, 2014; Goldfine, Victor, Conte, Bardin, & Schiff, 2011; Horki *et al.*, 2014). In this approach, the patient's engagement in the mental task is quantified by his or her ability to generate reliable, temporally and/or spatially specific modulations of brain activity identified in validation studies (Adapa, Davis, Stamatakis, Absalom, & Menon, 2014; Boly *et al.*, 2007; Davis *et al.*, 2007; Fernández-Espejo, Norton, & Owen, 2014; Naci, Cusack, Jia, & Owen, 2013; Owen & Coleman, 2007). A recent meta-analysis of studies comprising about 1,000 patients with disorders of consciousness indicated that approximately 15% of patients diagnosed as being in a Vegetative State exhibited so-called 'covert' command following in a neuroimaging-based assessment (Kondziella, Friberg, Frokjaer, Fabricius,

& Møller, 2016). Furthermore, these neuroimaging-based approaches have warranted the proposal of the non-behavioural Minimally Conscious State, which is indicated when a patient demonstrates covert command following alongside outward behaviour consistent with a Vegetative State (Gosseries, Zasler, *et al.*, 2014).

From a rehabilitation perspective, the ability to regulate one's brain activity in response to command could be fostered to eventually allow a suitable patient to communicate. Indeed, a few cases of fMRI-based communication by patients with disorders of consciousness have been reported using fMRI (Bardin, Schiff, & Voss, 2012; Fernández-Espejo & Owen, 2013; Forgacs *et al.*, 2014; Monti *et al.*, 2010; Naci & Owen, 2013). These findings raise the possibility that some patients diagnosed with disorders of consciousness could benefit from assistive devices known as brain-computer interfaces (Chatelle *et al.*, 2012; Gibson, Owen, & Cruse, 2016; Naci *et al.*, 2012). In brief, a brain-computer interface allows a person to operate a computer without producing a motor response. Subject-specific patterns of brain activity can be identified using machine-learning techniques and subsequently classified into predefined output, such as verbal responses of "yes" versus "no", or movement of a computer mouse cursor (Mason & Birch, 2003; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). Brain-computer interfaces based on EEG control signals are recommended for patients with disorders of consciousness because this signal can be non-invasively acquired at the bedside with low cost and few medical contraindications (Chatelle, Lesenfants, Guller, Laureys, & Noirhomme, 2015; Kübler & Kotchoubey, 2007; Naci *et al.*, 2012). To date, there are two especially noteworthy reports of EEG-based brain-computer interface use by patients with disorders of consciousness; four patients demonstrated modest improvements across time in a simple video game (moving a ball to a basket with motor imagery; Coyle *et al.*, 2015), and four other patients generated enhanced EEG markers of selective attention to target photos with feedback (Pan *et al.*, 2014). Ultimately, a brain-computer interface could provide a patient with a means to regulate his or her environment and communicate with other people. Moreover, the most consistently reported hope from family members of patients with disorders of consciousness is that the patient's ability to communicate will be restored (Jox *et al.*, 2015). From a clinical perspective, a patient is demonstrably capable of producing consistent and appropriate responses to commands by executing accurate brain-computer interface control. Accordingly, brain-computer interfaces for patients with disorders of consciousness can also fulfil the important diagnostic functions of cognitive assessment and awareness detection (Boly *et al.*, 2008; Kirschner, Cruse, Chennu, Owen, & Hampshire, 2015; Rodriguez Moreno, Schiff, Giacino, Kalmar, & Hirsch, 2010).

Unfortunately, there are at least three factors that restrict the development and anticipated literacy of neuroimaging techniques intended to restore communication with patients who have disorders of consciousness. Firstly, disorders of consciousness typically arise from severe and diffuse acquired brain injury (Bernat, 2006). As a consequence, the sensory and cognitive abilities of all patients with disorders of consciousness are potentially compromised by their brain injuries and other medical complications (Giacino *et al.*, 2014; Whyte *et al.*, 2013). For instance, patients with disorders of consciousness are susceptible to aphasia (Majerus, Bruno, Schnakers, Giacino, & Laureys, 2009), and many patients with disorders of consciousness lack oculomotor control (Kalmar & Giacino, 2005). Furthermore, the neural mechanisms that underlie the ability to covertly and overtly follow commands using mental imagery are distinct (Fernández-Espejo, Rossit, & Owen, 2015; Osborne, Owen, & Fernández-Espejo, 2015). Accordingly, patients with injuries to the necessary neural circuitry may be unable to generate the brain responses needed to covertly communicate via mental imagery, despite being able to perform other cognitive tasks. For these reasons, the mental tasks intended to provide a patient with a means to communicate should be customized to the patient's abilities. Consultation with caregivers and rehabilitation specialists, such as speech pathologists and occupational therapists, is also advised.

Secondly, it is difficult to use methods intended to detect covert command following as methods that support functional communication. For example, healthy volunteers recently participated in both the EEG- and fMRI-based assessments of command following previously discussed (Cruse *et al.*, 2011; Owen *et al.*, 2006). The sensitivities of these two techniques were directly compared (Gabriel *et al.*, 2015). In the fMRI assessments, most participants (85%) demonstrated covert command following, but few of the participants (60%) reliably communicated. Even fewer volunteers (30%) reliably communicated using EEG (Gabriel *et al.*, 2015). Additionally, many patients with disorders of consciousness generate brain responses that are variable over time and delayed relative to healthy volunteers (Bardin *et al.*, 2012; Fellinger *et al.*, 2011; Forgacs *et al.*, 2014). Single-trial decoding techniques commonly used with brain-computer interfaces have successfully identified some time-dependent changes in patient data (King *et al.*, 2013; Pokorny *et al.*, 2013; Sorger, Reithler, Dahmen, & Goebel, 2012). Unfortunately, these techniques are not yet widely used in assessments of covert command following. Alternative mental tasks and analysis techniques specifically developed for future use with brain-computer interfaces are therefore recommended to improve the likelihood that suitable patients with disorders of consciousness will communicate using their brain responses.

As a final consideration, it is not yet clear whether any level of confidence in neural data or brain-computer interface output will be sufficient for medical decision making (Bendtsen, 2013; Fins *et al.*, 2008; Mackenzie, 2013; Peterson *et al.*, 2013). For communicative applications, validation studies in healthy volunteers are necessary to ensure that the neural response of interest correlates with a volitional mental process. When these responses are subsequently assessed in patients, data quality must be carefully vetted. For example, most patients with disorders of consciousness lack voluntary motor control, and artefacts related to movement are common in their neural data. Similarly, data acquired at the bedside typically feature electrical noise from surrounding equipment that is especially problematic for EEG. In addition to these fundamental quality assurance measures, it is also necessary to quantify the likelihood that the patient generated a pattern of neural activity by chance (the null hypothesis), rather than in response to task demands (the alternative hypothesis). This quantification process is best achieved using an appropriate statistical analysis. At the time of writing, permutation testing is recommended to provide a confidence metric for the classification of medical information and the communicative output of a brain-computer interface (Billinger *et al.*, 2013; Cruse *et al.*, 2013; Goldfine *et al.*, 2013; Noirhomme *et al.*, 2014). Permutation testing estimates the distribution of the null hypothesis from the patient's neural data, and thus directly quantifies the likelihood that the observed data arose on the basis of chance (Maris & Oostenveld, 2007; Nichols & Holmes, 2002). All three of these measures are necessary to provide confidence in the quality and validity of any neural correlate of consciousness intended to inform patient care.

1.3 Summary and aims

Patients with disorders of consciousness exhibit profound behavioural impairments due to severe brain injury. Patients diagnosed as being in a Minimally Conscious State present with variable, but reproducible, responses to external stimulation (Giacino *et al.*, 2002). In contrast, patients in a Vegetative State exhibit no voluntary behaviour and lack awareness of all external stimulation (Bernat, 2006). These disorders are relatively uncommon, although reliable prevalence estimates are difficult to obtain due to variability in international diagnostic criteria and the heterogeneity of the patients themselves (Jennett, 2002; Pisa *et al.*, 2014). It is very unlikely (although not impossible) that a patient in a chronic Vegetative State will recover awareness (Multi-Society Task Force on PVS, 1994a, 1994b). Many of these patients remain severely disabled and completely dependent on others until the end of their lives (Bernat, 2006). Accordingly, the diagnosis of the Vegetative State carries significant legal and ethical consequences (Jennett, 2002).

Unfortunately, it is challenging to differentially diagnose disorders of consciousness. Careful, repeated assessments are needed to distinguish between reflexive or random responses and reliable, voluntary responses (Bernat, 2006; Kalmar & Giacino, 2005). Moreover, a patient's ability to respond may be comprised by many medical complications secondary to his or her brain injury (Whyte *et al.*, 2013). To this end, behavioural examinations have been complemented and supplemented by neuroimaging. Distinct neural correlates of minimal versus absent awareness have been identified (Giacino *et al.*, 2014; Laureys, 2005b; Owen, 2013). Most remarkably, a few patients diagnosed as being in a Vegetative State are able to appropriately and reliably modulate their brain activity in response to verbal commands (Bardin *et al.*, 2012; Cruse *et al.*, 2011; Goldfine *et al.*, 2011; Owen *et al.*, 2006). As many as 15% of patients who completely lack overt responsiveness exhibit this ability to covertly follow commands (Kondziella *et al.*, 2016).

A desirable next step for patients with disorders of consciousness is the restoration of their ability to communicate. The restoration of communication could allow patients to contribute to their care decisions and direct their activities of daily living (Jox *et al.*, 2015). Moreover, a patient's ability to communicate at the bedside may be restored with EEG-based techniques (Chatelle *et al.*, 2012; Naci *et al.*, 2012). Initial reports of successful EEG-based brain-computer interface control by patients with disorders of consciousness are promising (Coyle *et al.*, 2015; Pan *et al.*, 2014). However, patients have only communicated using fMRI-based techniques so far (Bardin *et al.*, 2012; Fernández-Espejo & Owen, 2013; Forgacs *et al.*, 2014; Monti *et al.*, 2010; Naci & Owen, 2013). For these reasons, the primary benefit of neuroimaging techniques for most patients with disorders of consciousness is cognitive assessment and awareness detection rather than communication *per se*.

The primary motivation of this thesis was the development and preliminary validation of EEG-based techniques to complement existing behavioural and fMRI-based assessments of patients with disorders of consciousness. All novel techniques were validated in healthy volunteers and patients with disorders of consciousness, and direct comparisons of EEG- and fMRI-based approaches were featured in all patient assessments. Furthermore, paradigms and analysis techniques were designed for future applications as brain-computer interfaces. Strategies to overcome the limitations of single-subject analyses of neuroimaging data using subject-specific mental tasks and distinct neural correlates are discussed in all chapters. Overall, this work provides novel advancements to the taxonomy of disorders of consciousness and the scientific understanding of consciousness via acquired brain injury. The specific aims and research questions of each experimental chapter are discussed in the following subsections.

1.3.1 Do complex and familiar actions enhance the neural correlates of mental imagery?

In brain-computer interface research involving motor imagery, volunteers are typically asked to imagine simple movements of their hands or feet (Kübler *et al.*, 2005; Neuper, Scherer, Wriessnegger, & Pfurtscheller, 2009; Pfurtscheller, Neuper, Brunner, & Lopes da Silva, 2005). Examples of such actions include squeezing one's hand into a fist and wiggling one's toes. Unfortunately, some healthy volunteers and patients with severe motor impairments are unable to sufficiently regulate their brain activity for brain-computer interface control during this type of motor imagery (Blankertz *et al.*, 2010; Guger, Edlinger, Harkam, Niedermayer, & Pfurtscheller, 2003; Hammer *et al.*, 2011). It has been proposed that brain responses to imagined familiar and complex actions may be more consistent and robust and hence comprise better control signals for brain-computer interface applications (Curran & Stokes, 2003). Indeed, the inclusion of a well-known sport (tennis) and a familiar environment (one's home) may have contributed to the success of the fMRI-based mental imagery tasks previously discussed for patients with disorders of consciousness (Owen *et al.*, 2006). Moreover, one of the EEG-based adaptations of that paradigm (Cruse *et al.*, 2011) may have lower sensitivity in healthy volunteers (Gabriel *et al.*, 2015) because the imagery tasks require participants to engage in simple imagined hand squeezes and toe wiggles rather than more familiar or complex actions.

The aim of Chapter 2 was to determine the influence of action complexity and familiarity on EEG-based motor imagery signals from healthy volunteers (Gibson, Chennu, Owen, & Cruse, 2014). Groups of experienced pianists, experienced ice hockey players, and novices performed motor imagery of actions from ice hockey and piano, alongside other common actions. Experienced athletes and musicians were selected for these experiments because the effects of motor learning are already well documented in these groups (Münte, Altenmüller, & Jäncke, 2002; Nakata, Yoshie, Miura, & Kudo, 2010). Indeed, expertise effects of motor learning in the brain are often described as enhanced efficiency; experienced athletes and musicians produce more focal patterns of brain activation than novices (Lotze, Scheler, Tan, Braun, & Birbaumer, 2003; Milton, Solodkin, Hlustík, & Small, 2007; Wei & Luo, 2010). It was accordingly predicted that healthy volunteers would generate brain responses that were more consistent in time for imagined familiar actions than for imagined unfamiliar actions. In terms of action complexity, imagery of actions that involve more complex motor sequences and multiple body parts correlates with greater hemodynamic changes in the brain and enhanced motor-evoked potentials, as compared to imagery of relatively simpler actions (Holper & Wolf, 2011; Kuhtz-Buschbeck *et al.*, 2003; Roosink & Zijdewind, 2010). It was hence predicted that complex motor imagery would correlate with more robust EEG responses than relatively simpler motor imagery, and that motor imagery of actions that were both complex and familiar would correlate with the most temporally reliable and robust EEG responses of all.

1.3.2 Do multiple mental imagery tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness?

Some patients with disorders of consciousness can volitionally modulate their brain activity by engaging in mental imagery during assessments with fMRI or EEG. However, patients with disorders of consciousness have acquired brain injuries and consequently vary in terms of their sensory and cognitive abilities. Indeed, brain injury may beget impairments in sensory processing, such as cortical blindness; sensory interpretation and motor output, as in agnosia, neglect, and apraxia; and higher-order cognition, including language and executive function (Anderson & Arciniegas, 2010; Satz, 1993). Patients with disorders of consciousness also vary in terms of their suitability for neuroimaging. For example, a patient cannot undergo an assessment with MRI if he or she cannot lie flat without suctioning for airway protection, or if he or she has certain types of metal implanted in his or her body. Likewise, a patient with a craniotomy (a surgical opening of the skull) is a poor candidate for assessment with EEG because the scalp above a skull breach generates aberrant EEG signals (Lee *et al.*, 2010). Furthermore, all patients with disorders of consciousness can be difficult to assess with neuroimaging because they lack voluntary motor control; many patients do not remain still long enough to generate images and other time series of sufficient quality for meaningful analysis. Accordingly, assessments of several cognitive abilities, supported by spatially distinct brain regions and indexed by multiple neural signatures, are needed to accurately characterise a patient's level of residual cognition and awareness (Gibson, Fernández-Espejo, *et al.*, 2014).

In Chapter 3, a small cohort of patients with disorders of consciousness participated in assessments intended to detect covert command following using fMRI- and EEG-based correlates of mental imagery (Gibson, Fernández-Espejo, *et al.*, 2014). The fMRI assessments included a motor imagery task ("imagine playing tennis") and a mental imagery task ("imagine visiting all the rooms in your house"; Owen *et al.*, 2006). These two tasks engage different mental processes and are associated with spatially distinct patterns of brain activation. Specifically, the motor imagery task requires the participant to imagine swinging a tennis racket to hit a ball very hard, while the spatial navigation task requires the participant to visualize the layout and contents of his or her home in sequence. Consequently, the motor task requires motor planning and is associated with activation of the supplementary motor area, while the spatial navigation task requires the retrieval of autobiographical memories and is associated with activation of the parahippocampal gyrus (Boly *et al.*, 2007; Monti *et al.*, 2010; Owen *et al.*, 2006). The EEG assessment in Chapter 3 included a conventional motor imagery task ("imagine squeezing your hand into a fist"; Cruse *et al.*, 2011) and a custom motor imagery task for each patient. During the custom motor imagery task, patients were asked to imagine performing an action from a sport or other activity identified as familiar to them by their caregivers. Together, these three assessments allowed for direct comparisons within and between mental processes (motor imagery and spatial navigation) and imaging modalities (fMRI and EEG). In light of the findings of Chapter 2, it was expected that familiar motor imagery would result in more reliable EEG responses than conventional motor imagery (Gibson, Chennu, *et al.*, 2014). More importantly, however, it was also expected that these distinct neural correlates of covert command following would provide corroborative evidence for each patient's residual cognitive abilities.

1.3.3 Does somatosensory attention identify awareness in patients with disorders of consciousness?

The abilities of some patients appropriately categorized as being in a Vegetative State or Minimally Conscious State vary along a continuum that is not necessarily apparent from their diagnosis. For example, some patients diagnosed as being in a Vegetative State exhibit reflexive startle responses to auditory and visual stimulation, while other patients do not respond to any external stimulation (Kalmar & Giacino, 2005). Just as a given patient's behavioural abilities can be quantified using specialized neuropsychological instruments, the neural correlates of a patient's abilities can also be characterised in a hierarchical fashion. For example, some patients diagnosed as being in a Vegetative State differentially process human speech as compared to signal-correlated noise, while other patients with the same diagnosis only differentially process sound and silence (Beukema *et al.*, 2016). Several other EEG-based techniques exist to characterise a patient's ability to engage in increasingly complex information processing (*e.g.*, Bekinschtein *et al.*, 2009; Chennu *et al.*, 2013; Faugeras *et al.*, 2012; Fischer, Luaute, & Morlet, 2010; Kotchoubey *et al.*, 2005). Unfortunately, there are inconsistencies in the prognostic value of these techniques; for example, some investigators have reported positive prognostic value in EEG markers of higher-order attentional processing (Lew *et al.*, 2003), while others have not (Steppacher *et al.*, 2013). These discrepancies may have occurred because patients with the ability to covertly follow commands (*i.e.*, those in a non-behavioural Minimally Conscious State) were not identified, or because all approaches primarily relied upon auditory information (Gibson, Chennu, *et al.*, 2016).

The aim of Chapter 4 was to assess covert cognition in patients with disorders of consciousness using multi-modal assessments of covert command following and attentional processing (Gibson, Chennu, *et al.*, 2016). The patients underwent neuroimaging-based assessments of command following using fMRI. Specifically, the patients completed the spatial navigation and tennis imagery paradigms previously described (Owen *et al.*, 2006). Additionally, all patients participated in a novel EEG paradigm intended to delineate a hierarchy of attentional processing using vibrotactile stimulation. Healthy volunteers completed the same vibrotactile attention task as a validation measure. Finally, all patients also completed an fMRI-based auditory selective attention task. The auditory selective attention paradigm has already been validated in patients with disorders of consciousness and healthy volunteers (Naci *et al.*, 2013; Naci & Owen, 2013). Furthermore, the auditory selective attention task has similar demands as the EEG-based vibrotactile attention paradigm and thus provided an additional validation measure for the EEG approach. As in Chapter 3, it was expected that these distinct neural correlates of covert cognition would provide strong evidence for each patient's abilities. Finally, it was also expected that the novel EEG technique would corroborate the identification of patients with the ability to covertly follow commands.

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Chapter 2

2 Complexity and familiarity enhance single-trial detectability of imagined movements with electroencephalography

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Gibson, R. M., Chennu, S., Owen, A. M., & Cruse, D. (2014). Complexity and familiarity enhance single-trial detectability of imagined movements with electroencephalography. *Clinical Neurophysiology*, *125*, 1556–1567. http://dx.doi.org/10.1016/j.clinph.2013.11.034

2.1 Introduction

A particular EEG signal called the sensorimotor rhythm is a practical option for brain-computer interfaces intended for use by patients with disorders of consciousness (Chatelle *et al.*, 2012; Naci *et al.*, 2012). Using as few as four surface electrodes placed over sensorimotor cortical areas, one can acquire a sensorimotor rhythm as a person kinaesthetically imagines moving a body part. Sensorimotor rhythms are quantified as power decreases known as event-related desynchronizations and power increases known as event-related synchronizations. Sensorimotor rhythms occur in the mu (7−12 Hz) and beta (13−30 Hz) frequency bands of the human electroencephalogram (Neuper & Pfurtscheller, 2001; Pfurtscheller & Neuper, 1997). Unlike other EEG-based brain-computer interface paradigms, the imagination tasks used with sensorimotor rhythm-based brain-computer interfaces impose low sensory demands on the user. Of particular importance for patients who are unable to fixate their eyes, sensorimotor rhythm-based brain-computer interfaces need not involve visual stimulation (Chatelle *et al.*, 2012; Grosse-Wentrup & Schölkopf, 2013; Naci *et al.*, 2012). Patients with chronic and extensive motor impairments, including tetraplegia and advanced Amyotrophic Lateral Sclerosis, can control sensorimotor rhythm-based brain-computer interfaces (Kübler *et al.*, 2005; Pfurtscheller, Guger, Müller-Putz, Krausz, & Neuper, 2000). Indeed, patients diagnosed as being in a Vegetative State or Minimally Conscious State can produce sensorimotor rhythms during motor imagery, even after several years of immobility (Cruse *et al.*, 2011; Goldfine, Victor, Conte, Bardin, & Schiff, 2011; Horki *et al.*, 2014). Owing in part to this ease of use by patients, brain-computer interfaces based on responses to motor imagery were the most widely studied type of brain-computer interface between 2007 and 2011 (Hwang, Kim, Choi, & Im, 2013).

Despite the potential benefits of bedside sensorimotor rhythm-based brain-computer interfaces for patients with disorders of consciousness, there is substantial intra- and inter-subject variability in sensorimotor rhythm-based brain-computer interface performance (Naci *et al.*, 2012; Pfurtscheller, Brunner, Schlögl, & Lopes da Silva, 2006; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). For reliable communication, classification accuracy of 70% is regarded as the lower limit of acceptable performance (Kübler *et al.*, 2001). In 2003, about 49 of 100 healthy volunteers did not achieve performance accuracy above 70% with a simple sensorimotor rhythm-based brain-computer interface (Guger, Edlinger, Harkam, Niedermayer, & Pfurtscheller, 2003). In 2011, modest improvements were evident in an updated sensorimotor rhythm-based brain-computer interface paradigm, such that only 30 of 80 volunteers did not achieve performance accuracy above 70% (Hammer *et al.*, 2011). Unfortunately, some healthy volunteers and patients are still unable to achieve sufficient brain-computer interface control for communication via motor imagery, even using state-of-the-art sensorimotor rhythm-based brain-computer interfaces with optimized feedback protocols and online processing of the EEG data (*e.g.*, Ang & Guan, 2017; Roussel, Negishi, & Mitsukura, 2016; Sollfrank *et al.*, 2016). This phenomenon is sometimes referred to as brain-computer interface illiteracy, and it is estimated to affect about 10 to 30% of potential healthy users (Vidaurre & Blankertz, 2010). Brain-computer interface illiteracy is especially problematic for devices intended to restore communication to patients with disorders of consciousness because only a small portion (15%) of these patients are likely to have the covert cognitive abilities needed for brain-computer interface control (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016).

To address brain-computer interface illiteracy, some researchers have proposed that alterations should be made to the mental tasks used to drive sensorimotor rhythm-based brain-computer interfaces (Curran *et al.*, 2004; Curran & Stokes, 2003; Scherer *et al.*, 2015). In published sensorimotor rhythm-based brain-computer interface research to date, users are typically instructed to imagine moving their hands, feet, or tongue (Kübler *et al.*, 2005; Neuper & Pfurtscheller, 2001; Pfurtscheller *et al.*, 2006). With only a few exceptions, users are asked to imagine very simple actions, such as repeatedly squeezing one of their hands into a fist. However, actions that are more complex or familiar could result in a more robust and consistent sensorimotor rhythm (Curran *et al.*, 2004; Curran & Stokes, 2003). Similarly, comparisons in traditional sensorimotor rhythm-based brain-computer interface research are often made between the sensorimotor rhythms generated for different imagined movements, such as the left versus right hands (Cruse *et al.*, 2011; Guger *et al.*, 2003; Kübler *et al.*, 2005). Although these comparisons render acceptable classification accuracy in most healthy people (Bai *et al.*, 2008; Guger *et al.*, 2003), these types of comparisons may not be optimal for patients diagnosed with disorders of consciousness. Indeed, a patient's ability to exhibit a particular voluntary action in response to command is the criteria for awareness during the administration of the Coma Recovery Scale (Kalmar & Giacino, 2005). If the patient is able to successfully demonstrate that action on three out of four occasions, the patient is diagnosed as at least minimally conscious (Kalmar & Giacino, 2005). Accordingly, contrasts in this chapter were made between one imagined action and periods of rest (mind-wandering), rather than between two distinct imagined actions. This technique is more practical for patients who are behaviourally non-responsive because sustaining more than one imagined action in working memory may impose excessive cognitive demands on some patients. Furthermore, this technique allows for an EEG-based assessment that is similar to standard clinical tools.

In a series of three experiments, healthy, young adults imagined actions of varying complexity and familiarity during EEG recordings. All tasks employed an experimental set-up suitable for future clinical applications at the bedside. It was hypothesized that motor imagery involving more complex and familiar movements than previous investigations would improve classification accuracy and result in more users with sensorimotor rhythms that could be reliably detected. If supported, the hypotheses of these three experiments could be extended to future clinical work with imagery tasks catered to the skills and hobbies of the target patient user.

In Experiment 1 (Complexity), participants imagined simple hand actions (squeezes) of the sort typically used with sensorimotor rhythm-based brain-computer interfaces, alongside other more complex bimanual actions. Following previous work, "complex" motor imagery is defined as imagined actions that involve sequences of movements and more than one body part (Holper & Wolf, 2011). In accordance with prior evidence of increased brain activity during complex motor imagery (Holper & Wolf, 2011; Kuhtz-Buschbeck *et al.*, 2003; Roosink & Zijdewind, 2010), it was predicted that classification accuracy (versus rest) would be higher when the participant imagined complex actions than when the participant imagined relatively simpler actions.

In Experiment 2 (Familiarity), groups of experienced pianists, experienced ice hockey players, and age-matched controls imagined squeezing their hands and performing actions from hockey and piano. This experiment featured experienced athletes and musicians because the effects of long-term motor learning have been extensively studied in these groups (Münte, Altenmüller, & Jäncke, 2002; Nakata, Yoshie, Miura, & Kudo, 2010). Relative to novices, experienced athletes and musicians produce more focused patterns of brain activation (Lotze, Scheler, Tan, Braun, & Birbaumer, 2003; Milton, Solodkin, Hlustík, & Small, 2007; Olsson, Jonsson, Larsson, & Nyberg, 2008; Wei & Luo, 2010). Expert athletes and musicians also report more objectively accurate imagery than novices (Louis, Collet, Champely, & Guillot, 2012; Rieger, 2012). Accordingly, it was predicted that classification accuracy between rest and imagery would be highest for the athletes and musicians during the action with which they were most familiar, *i.e.,* pianists imagining playing the piano, and hockey players imagining playing hockey (Fourkas, Bonavolontà, Avenanti, & Aglioti, 2008; Lotze *et al.*, 2003; Olsson *et al.*, 2008; Wei & Luo, 2010).

In Experiment 3 (Complexity and Familiarity), a potential synergistic influence of imagined action complexity and familiarity on the sensorimotor rhythm was examined.

Specifically, the experienced pianists from Experiment 2 imagined playing one simple piece of music and one relatively more complex piece of music on the piano. It was expected that classification accuracy would be highest for the complex piece versus rest comparison.

2.2 Materials and methods

2.2.1 Participants and stimuli

2.2.1.1 Experiment 1: Complexity

Sixteen healthy, right-handed young adults participated in the complexity study (five men; age range=17-20 years; median age of 18 years). For the simple imagined movement phase, the participants were instructed to imagine repeatedly squeezing their left hand, right hand, or both hands following the auditory cues of “left”, “right”, and “both”, respectively. For the complex imagined movements phase, the participants were instructed to imagine either playing the guitar, clapping their hands, or juggling using both hands. These tasks were cued with the words “guitar”, “clap”, and “juggle”, respectively. In each task phase, participants were also asked to mind-wander following the cue “relax”. The order of the simple and complex imagined movement phases was counter-balanced across participants. All auditory instructions were 1-second in length.

2.2.1.2 Experiment 2: Familiarity

Forty-eight healthy, right-handed young adults participated in the familiarity study. Sixteen participants were experienced ice hockey players (seven men; age range=18-29 years; median age of 20 years); sixteen participants were experienced pianists (six men; age range=18-29 years; median age of 20 years); and sixteen participants had either limited or no experience playing the piano or hockey (eight men; age range=18-28 years; median age of 18 years). All hockey players had regularly played competitive ice hockey for at least ten years. All pianists had formal musical training and had regularly played and practiced piano for at least ten years.

There were no significant differences in mean age of first play experience, mean years of total play experience, or mean self-reported hours of regular play per week between the groups of athletes and musicians, pairwise *p*s>.51 (Bonferroni correction; Table 3). There were also no group differences in handedness (Oldfield, 1971), imagery ability (Gregg, Hall, & Butler, 2010), age, or sex, *p*s >.34 (Table 3). All participants were instructed to imagine making a slap shot (a bimanual action from hockey), playing a musical piece on the piano using both hands, or squeezing their right hand into a fist following the auditory cues of “hockey”, “piano”, and “right hand”, respectively. As in Experiment 1, participants were asked to mind-wander following the cue “relax”, and all instructions were 1-second in length.

2.2.1.3 Experiment 3: Complexity and Familiarity

The experienced pianists (*n*=16) from Experiment 2 completed Experiment 3 in the same recording session. In Experiment 3, the pianists were instructed to imagine playing ascending and descending C-major scales and B-major arpeggios over two octaves using both hands following the auditory cues of “scale” and “arpeggio”. The pieces of music were selected based on the curriculum of the Royal Conservatory of Music, which is a prominent musical education institution in Canada. In this curriculum, piano students are evaluated on scales and the key of C-major from the first grade level; arpeggios from the fourth grade level; and the key of B-major from the seventh grade level (Royal Conservatory of Music, 2008). Given the different grade levels at which the C-major scale and B-major arpeggio are evaluated in the Royal Conservatory of Music curriculum, the B-major arpeggio represents a more complex action than the C-major scale. The pianists reported high familiarity with both pieces and recalled both pieces from memory. As in Experiment 1, the participants were instructed to mind-wander following the cue “relax”, and all instructions were 1-second in length. The Experiment 3 procedure was always conducted following the Experiment 2 procedure to prevent pianists from selecting the musical pieces from Experiment 3 for the piano imagery in Experiment 2.

Table 3. Demographic and other measures for Experiments 2 and 3 of Chapter 2.

Variable	Pianists	Hockey Players	Controls	Total
	M ± *SD*	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*
Demographics				
n	16	16	16	48
Sex (# male)	6	7	8	21
Age (years)	20.6 ± 2.9	20.9 ± 3.4	19.4 ± 2.7	20.3 ± 3.0
Laterality Quotient [a]	70.9 ± 14.7	70.9 ± 21.9	67.8 ± 20.7	69.9 ± 19.0
Hockey Experience [b]				
Initial age (years)	1.6 ± 3.0	5.0 ± 1.7[*, b]	2.6 ± 4.2	3.1 ± 3.4
Total years	0.9 ± 1.8	15.4 ± 3.4[***]	0.4 ± 0.9	5.6 ± 7.4
Hours per week	0.5 ± 2.0	9.2 ± 4.5[***]	0.8 ± 2.0	3.5 ± 5.1
Number of other sports played	1.5 ± 1.2	2.9 ± 1.5[*]	2.4 ± 1.6	2.3 ± 1.5
Piano Experience [c]				
Initial age (years)	5.4 ± 2.0[†]	1.6 ± 3.4	3.7 ± 6.7	3.6 ± 4.7
Total years	14.8 ± 3.6[***]	0.5 ± 1.2	0.6 ± 1.4	5.3 ± 7.1
Hours per week	8.9 ± 3.8[***]	0.3 ± 0.7	0.6 ± 1.3	3.2 ± 4.7
Number of other instruments played	1.6 ± 1.0[***]	0.3 ± 0.5	0.7 ± 0.6	0.9 ± 0.9
Imagery Ability [d]				
Kinaesthetic	5.2 ± 1.0	5.1 ± 1.1	4.8 ± 1.3	5.0 ± 1.1
Visual	5.8 ± 1.0	5.6 ± 1.4	5.4 ± 1.0	5.6 ± 1.1
Self-report ratings of imagery				
Vividness [e]	3.9 ± 1.0 [f]	3.7 ± 0.6	3.8 ± 0.7	3.8 ± 0.8
	4.2 ± 1.1 [g]			

Notes. M=mean; *SD*=standard deviation.

[a] The Laterality Quotient is a measurement of handedness (Oldfield, 1971).

[b] Four pianists reported some leisure experience playing hockey (2-5 years total experience initiated at ages 5-8), and four controls reported some leisure experience playing hockey (1-3 years total experience initiated at ages 5-13).

[c] Three hockey players reported some leisure experience playing piano (1-4 years total experience initiated at ages 7-10), and five controls reported some leisure experience playing piano (0.5-5 years total experience initiated at ages 5-22).

[d] Performance on the Movement Imagination Questionnaire-Revised Second version (Gregg *et al.*, 2010)

[e] Responses to the following question: "Please rate the overall vividness of your imagined actions during the task, such that: 1=not at all vivid, 2=slightly vivid, 3=somewhat vivid, 4=moderately vivid, 5=very vivid"

[f] Responses from the pianists for the Experiment 2 imagery

[g] Responses from the pianists for the Experiment 3 imagery

[***]$p<.001$; [*]$p<.05$; [†]$p<.1$.

2.2.2 Procedure

Before the EEG recording session, each participant completed a series of questionnaires. All participants completed the Edinburgh Handedness Inventory (Oldfield, 1971) and the Movement Imagery Questionnaire-Revised Second version (Gregg *et al.*, 2010). Participants in Experiments 2 and 3 also completed a questionnaire regarding their experiences playing hockey, piano, and other sports and instruments. After Experiments 2 and 3, participants rated the vividness of their imagined actions using a 5-point Likert scale (Table 3).

All auditory cues were pre-recorded by a female speaker and presented to the participant using ER-1 insert earphones (Etymōtic Research Inc., Elk Grove Village, IL). Each trial began with an auditory cue and was followed by 5 to 8 seconds of silence before the onset of the next auditory cue. The duration of the silent interval was randomly selected from a uniform distribution on each trial. Experiments 1 and 2 were completed in four blocks of 48 trials (12 trials of each instruction per block). Experiment 3 was completed in three blocks of 48 trials (16 trials of each instruction per block), as there were only three (rather than four) trial types in the latter task. Each block of 48 trials was approximately six minutes in duration. All trials were presented in a pseudorandom order such that no more than two cues of the same type were consecutively presented, and the first trial of each block was always an imagined action trial (rather than a ‘relax’ trial). Participants were provided with short breaks between blocks to reduce fatigue. Participants were also instructed to imagine completing each action repeatedly from the offset of the auditory cue to the onset of the next auditory cue. This instruction was intended to account for potential differences in the duration of the imagined actions.

2.2.3 Data acquisition and pre-processing

In all three studies, the EEG data were recorded using the g.Gamma active electrode system (g.tec Medical Engineering GmbH, Austria). In Experiment 1, the EEG data were recorded with a four-channel montage housed in an electrode cap; the electrodes were placed at sites CP3, FC3, CP4, and FC4 (Sharbrough *et al.*, 1991). In Experiments 2 and 3, the EEG data were recorded from the same four scalp sites as in Experiment 1, and additional electrodes were placed at sites TP7, FT7, CPz, FCz, TP8, and FT8 (Sharbrough *et al.*, 1991). The reported analyses for Experiments 2 and 3 consist of data from only the four electrodes used in Experiment 1, following previous work (Cruse *et al.*, 2012; Guger *et al.*, 2003).

The EEG signals were acquired using a g.USBamp amplifier operating through a USB 2.0 port. Stimuli presentation and physiological data recordings were performed using a Simulink® model in Matlab (Mathworks, Inc., Natick, MA). Simulink® ensures the precise synchronization of EEG activity with cue onset/offset (Guger *et al.*, 2001). In all three studies, bipolar surface electromyographic recordings were obtained from the ventral surface of the forearms to detect overt movements. Online, the EEG data were filtered from 0.5 to 60 Hz with a 60 Hz notch filter using an infinite impulse response digital Butterworth filter. The electromyographic data were filtered from 5 to 250 Hz with a 60 Hz notch filter. The EEG recordings were referenced to the right earlobe with a forehead (Fpz) ground, and the right elbow was used for the electromyographic ground. All data were sampled at 600 Hz with impedances below 5 kΩ at the beginning of the EEG recording.

Offline data processing was conducted with EEGLAB (Delorme & Makeig, 2004). The EEG data were down-sampled to 100 Hz, filtered between 0.5 and 40 Hz using the EEGLAB function ‘pop_eegfilt’, and segmented into 6-second epochs time-locked to the onset of the auditory cue. The EEGLAB filter function consisted of a two-step least-squares finite impulse response filter. The data were first filtered with a high-pass cut-off of 0.5 Hz, and the data were then filtered with a low-pass cut-off of 40 Hz. The electromyographic data were rectified and then filtered with a 10 Hz high pass filter using the same EEGLAB least-squares filter function previously described. Trials containing physiological artefacts, including overt hand movements as evident from the electromyographic data, were identified by visual inspection and removed. After artefact rejection, the median number of trials included in each imagery and rest condition per participant was: 40 in Experiment 1 (range=29−48); 43 in Experiment 2 (range=27−48); and 43 in Experiment 3 (range=28−48). Finally, the EEG data were re-referenced offline to form two bipolar channels (FC3−CP3, FC4−CP4) that are subsequently identified as C3' and C4', respectively.

2.2.4 Single-trial classification

A machine-learning algorithm was used for single-trial classification of the EEG data (Cruse *et al.*, 2011, 2012). For these analyses, the log band power values of four frequency bands at electrodes C3' and C4' were the classification features. Based on previous work (Cruse *et al.*, 2011, 2012), the frequency bands were: 7 to 13 Hz (mu); 13 to 19 Hz (low-beta); 19 to 25 Hz (mid-beta); and 25 to 30 Hz (high-beta), for a total of eight features per classification analysis (two electrodes x four frequency bands). For the single-trial analyses, the spectral power in each band was estimated with a sliding 1-second Hamming window moving in 50-ms steps and using a short time Fourier transform (Matlab function 'spectrogram'; Pfurtscheller & Lopes da Silva, 1999).

Classification of each imagined action and the corresponding rest condition was performed using a naïve Bayes classifier (Matlab's 'naivebayes' object). Each classification analysis was conducted using ten-fold cross-validation. For the cross-validation procedure, each participant's trials for one type of imagined action and the rest condition from the same experiment were separated into ten groups approximately equal in size. The naïve Bayes classifier was trained on the features of nine of these groups (training), and then the class of each trial in the tenth group was predicted to calculate the classifier's accuracy (testing). Specifically, during training, the naïve Bayes classifier estimated the parameters of a probability distribution per training feature per class. The parameters of this probability distribution were the mean and standard deviation of a normal distribution; the training features were power per frequency band at each electrode; and the two classes were the rest and imagery trial types. Using Bayes' Theorem during testing, the features of the test trials were used to calculate the posterior probabilities for each class, and then each test trial was placed in the class with the highest posterior probability (Jiang, Wang, Cai, & Yan, 2007). The classification procedure was repeated ten times so that each trial served as a test trial in exactly one of the ten cross-validation folds. The average classification accuracy across the ten folds was then calculated at each time-point. Finally, the time-course of the cross-validated classification accuracy was smoothed with a sliding window of 500 ms to control for outliers (Cruse *et al.*, 2012).

To determine the statistical significance of the classification accuracy, a permutation test with 1,000 repetitions was used (Cruse *et al.*, 2012; Maris, 2004). For each permutation, the class labels of imagery or rest were shuffled across trials, and the cross-validated classification procedure previously described was repeated. The maximum smoothed accuracies across all time-points from each of the 1,000 repetitions were used to form a distribution representing the expected classification results if the classifier were operating at chance (the null hypothesis). The classification accuracy obtained for the participant's original data (*i.e.*, the data with the correct trial labels) was then evaluated against this distribution. This comparison step enabled the calculation of a familywise error-corrected significance value for the original classification results at each time-point. Finally, to control for the multiple comparisons of band power (*i.e.*, one comparison for each time point of imagery versus rest), a control of False Discovery Rate approach was used implemented via Matlab's 'fdr' function (Benjamini & Hochberg, 1995; Verhoeven, Simonsen, & Mcintyre, 2005). The control of False Discovery Rate approach reduces the risk of Type I error without requiring as stringent reductions in power as Bonferroni procedures (Verhoeven *et al.*, 2005).

2.2.5 Time-frequency analyses

In addition to the single-trial classification analyses of the data, the EEG data from all three studies were analysed using the same spectral analysis procedure reported elsewhere (Cruse *et al.*, 2012). For each time-point at C3' and C4', spectral power estimates were calculated using a 1-second Hanning window time-frequency transformation via the 'ft_freqstatistics' function of the open-source Matlab toolbox, FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011). The time-frequency data at both electrodes were then compared between the imagined movements and rest using cluster-based permutation testing implemented via FieldTrip (Cruse *et al.*, 2012; Maris & Oostenveld, 2007). For the cluster-based testing, the time-frequency data for a given imagery condition and rest (or another imagery condition, as in Experiment 3) were log-transformed and then compared at each data point by a paired-samples *t* test. All significant data points (p<.025) were then arranged into groups, *i.e.*, clusters, based on their temporal and spectral proximity to each other. The sum of the t values was then calculated for each cluster. To determine the familywise error-corrected significance for each summed t value, a Monte Carlo randomization test that controlled for familywise error was used. In the randomization test, the condition labels were permuted to remove task-related differences, and the clustering procedure was repeated 1,000 times. The maximum summed clusters from these repetitions were used to form a distribution, and this distribution was then used to test the null hypothesis that the original summed t value (*i.e.*, the summed t value computed from the data with the correct trial labels) occurred by chance.

2.2.6 Group-level statistics

For the single-trial analyses of the EEG data, all group-level statistical analyses were conducted using IBM SPSS Statistics version 21.0. The Dunn-Sidak correction was used for the follow-up tests. For the spectral analyses of the EEG data, all statistical analyses were conducted using the cluster-based permutation testing previously described via custom Matlab script and FieldTrip (Cruse *et al.*, 2012; Maris & Oostenveld, 2007; Oostenveld *et al.*, 2011).

For the group comparisons of the single-trial analyses, several parametric and non-parametric repeated-measures statistical tests were used. Paired-samples t tests were used to compare maximum classification accuracy and the time at which maximum classification accuracy occurred relative to the onset of the instruction in both Experiments 1 and 3. Wilcoxon Signed Rank Tests were used to compare the number of time-points for which a statistically reliable classification was obtained in the same two studies. This test was also used to compare the self-reported vividness ratings of the imagined actions from the pianists between Experiment 2 and Experiment 3. An exact (rather than asymptotic) calculation of the p value was used with the test of time-points in Experiment 1 to account for the positive skew of the count data (given that many participants had zero statistically reliable time-points). Finally, the number of trials included in each complexity condition of each study was compared using the Friedman test.

To further illustrate the difference between the single-trial analyses of the complexity effects in Experiments 1 and 3, participants were assigned to a binary category based on whether at least one imagined movement in each complexity condition was classified from rest with a statistically reliable result (0=no statistically reliable classifications). The number of participants with at least one statistically reliable classification and the number of participants with no statistically reliable classifications in each complexity level were then compared using Fisher's Exact Test.

For Experiment 2, three separate 3 (Group: Pianist, Hockey, Control) x 3 (Action: Play Piano, Slap-shot, Squeeze) mixed analyses of variance were used to compare the averaged maximum classification accuracies, the time at which the maximum accuracy occurred, and the total number of trials included in each condition (*N.B.*, the trial numbers were rank-transformed to meet the statistical assumptions of the analysis). Additionally, a Kruskal-Wallis test was performed to compare the self-reported imagery vividness ratings between the groups. Given that classification accuracy did not statistically differ between conditions in Experiment 2, no comparisons were made for the number of time points that were classified with a statistically reliable result.

The group spectral analyses were conducted with the time-frequency data averaged across all trials in each condition per participant. For Experiment 1, the time-frequency data for each participant were averaged across the three imagined actions in each of the two complexity levels, *i.e.,* simple and complex imagery. The cluster-based permutation testing was then conducted between each complexity level and rest, and between the two complexity levels (Figure 1). For Experiment 2, comparisons were separately made for each familiarity group between each imagery condition and rest (Figure 3). For Experiment 3, comparisons were made between each of the two imagery conditions and rest, and between the two imagery conditions (Figure 4). *Post-hoc* comparisons were also conducted between the piano imagery in Experiments 2 and 3.

2.3 Results

2.3.1 Experiment 1: Complexity

In terms of the single-trial analyses of the EEG data, there was a trend for classification accuracy to be higher for the complex imagined actions than the simple imagined actions, $t(15)=-1.963$, $p=.068$, $d=0.49$ (Simple: *Mean(M)*=60.68%, *Standard Error (SE)*=0.74%; Complex: *M*= 62.74%, *SE*=0.93%). There was no statistical difference for the time at which the maximum classification accuracy occurred between the two complexity conditions, $p=0.29$. From the familywise permutation tests, there were more time-points at which statistically reliable classifications were obtained in the complex condition than in the simple condition, $Z=-2.197$, exact $p=.026$, $r=.55$ (Simple: median of zero statistically reliable time-points [range: 0-26]; Complex: median of 14.5 statistically reliable time-points [range: 0-31]). There was also no statistically reliable difference in the number of trials in the two complexity levels, $p=.29$.

There was some variability between and within subjects for the single-trial analyses. While at least one simple imagined action type was classified from rest with a statistically reliable outcome for only four of the participants (25% of the sample), at least one complex imagined action type was classified from rest with a statistically reliable outcome for more participants (11 of 16, or 69%), Fisher's exact $p=.032$ (two-tailed). Notably, there were some participants in the sample who did not produce any statistically reliable sensorimotor rhythms for any of the imagined actions (25% of the sample). This portion of the sample could reflect the estimated 10 to 30% of users designated as 'brain-computer interface illiterate' in previous work (Vidaurre & Blankertz, 2010). The inter- and intra-subject variability in classification accuracy is summarized in Table 4 and detailed in the supplementary data tables (Appendix C).

Table 4. Summary of the single-trial classification outcomes in Chapter 2.

Experiment 1 (Complexity; *n*=16)

Simple Imagery

	Right Hand vs. Rest				Left Hand vs. Rest				Both Hands vs. Rest			
	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s
M	60.61	2.59	3.63	2	60.15	2.22	1.75	1	61.27	2.85	6.25	4
SE	0.97	0.29	2.50	-	0.70	0.37	0.94	-	0.93	0.33	3.46	-

Complex Imagery

	Juggle vs. Rest				Guitar vs. Rest				Clap vs. Rest			
	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s
M	62.71	2.79	9.31	8	63.83	2.42	15.06	7	61.67	2.44	6.06	7
SE	1.07	0.24	3.67	-	1.58	0.32	6.19	-	1.23	0.33	2.63	-

Experiment 2 (Familiarity; *n*=48)

	Piano vs. Rest				Hockey vs. Rest				Hand Squeeze vs. Rest			
	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s
Pianists (*n*=16)												
M	63.31	2.76	16.31	7	62.74	2.27	9.88	8	60.76	2.45	6.19	7
SE	1.49	0.24	5.99	-	1.38	0.35	4.69	-	1.05	0.33	2.96	-
Hockey Players (*n*=16)												
M	59.23	2.25	3.88	4	60.34	2.31	5.50	4	59.52	2.35	4.69	4
SE	0.98	0.31	1.95	-	1.64	0.24	2.95	-	1.02	0.28	2.80	-
Controls (*n*=16)												
M	63.12	2.35	12.94	8	63.75	2.18	11.69	9	63.69	2.25	12.06	8
SE	1.49	0.27	5.70	-	1.38	0.26	4.82	-	1.37	0.33	4.53	-

Experiment 3 (Complexity and Familiarity; *n*=16)

	Simple Music (Scale) vs. Rest				Complex Music (Arpeggio) vs. Rest			
	Maximum Accuracy	Time of Maximum	Duration	n_s	Maximum Accuracy	Time of Maximum	Duration	n_s
M	66.34	2.61	23.19	9	69.60	2.51	33.69	13
SE	1.96	0.19	7.18	-	2.03	0.28	7.10	-

Notes. Maximum Accuracy=maximum cross-validated classification accuracy (%); Time of Maximum=time at which Maximum Accuracy occurred (seconds following the offset of the auditory cue); Duration=number of time points for which statistically reliable classification results were obtained; n_s=number of participants for which statistically reliable classifications were obtained; *M*=mean; *SE*=standard error.

From the group spectral analyses of the EEG data (Figure 1), there were statistically reliable event-related desynchronizations over the left hemisphere in the low-beta band in the complex imagery versus rest comparison (*p*s<.014). In the simple imagery versus rest comparison, there was an event-related desynchronization over the right hemisphere in the mid-beta band that approached statistical significance (*p*=.050). Additionally, there were no statistically reliable clusters in the simple imagery versus complex imagery comparisons (*p*s>.10).

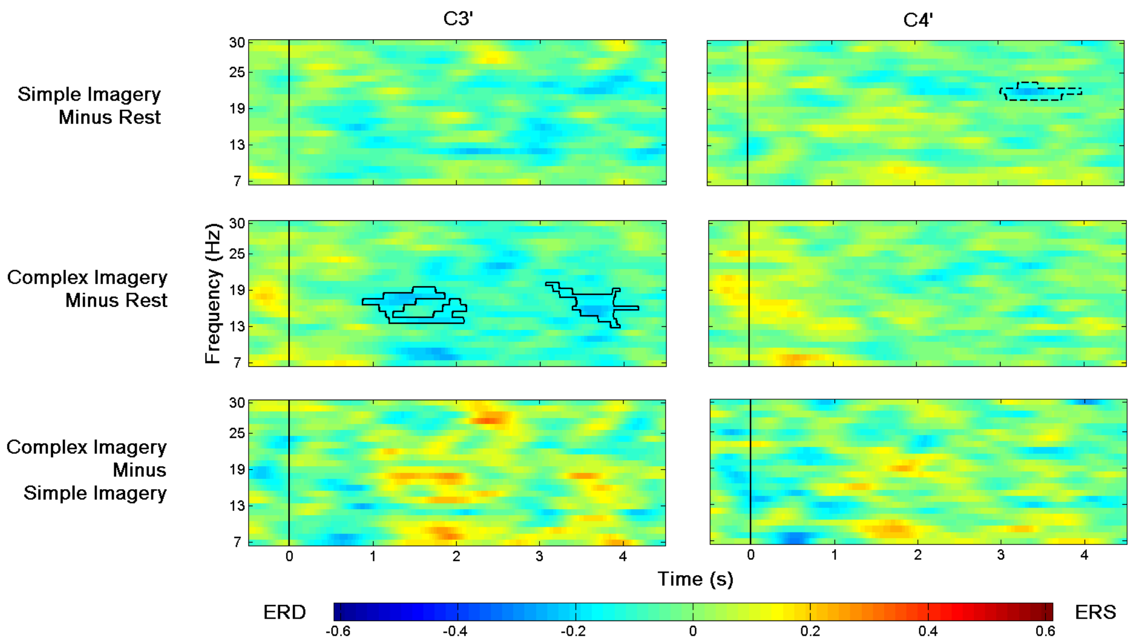

Figure 1. Outcomes of the group spectral analyses in Experiment 1 of Chapter 2.

Averaged, group (*n*=16) time-frequency plots from the spectral analyses of the EEG data for Experiment 1 (Complexity) averaged across the three imagined actions in each imagery condition. The range of power values (log ratio difference) that are plotted is ±0.6121. Significant clusters (*p*s<.014) are outlined with solid lines; dashed lines highlight a cluster with *p*=.050. Time is measured relative to the offset of the instruction.

Although the role of action familiarity was not explicitly examined in Experiment 1, there was one interesting finding in this experiment that emphasized the potential influence of prior experience on single-subject performance. In Figure 2, the time-course of the single-trial classification accuracies for one of two experienced guitarists who participated in Experiment 1 is depicted. In line with the group trends already reported, these participants did not produce sensorimotor rhythms that were classified from rest with statistical reliability for any of the simple imagined actions. The averaged, maximum classification accuracy obtained for these participants during simple motor imagery was 57.58% (*SE*=1.01%). Moreover, the classification results for the simple imagery versus rest comparisons were not statistically reliable at any time-point for either participant. Both participants produced sensorimotor rhythms for the instruction to imagine clapping that were reliably classified from rest for a short time (six to seven time-points with smoothed maximum classification accuracy of 64.79%±3.52%, no figure provided, and 64.47%±4.04%, as shown in Figure 2). Most interestingly, however, both participants produced a markedly robust sensorimotor rhythm for the instruction to imagine playing the guitar. These sensorimotor rhythms were classified from rest for most of the epoch (68-69 time-points) with very high accuracy (maximum accuracies of 81.10%, *SE*=3.44%, as shown in Figure 2, and 71.28%, *SE*=3.97%, no figure provided).

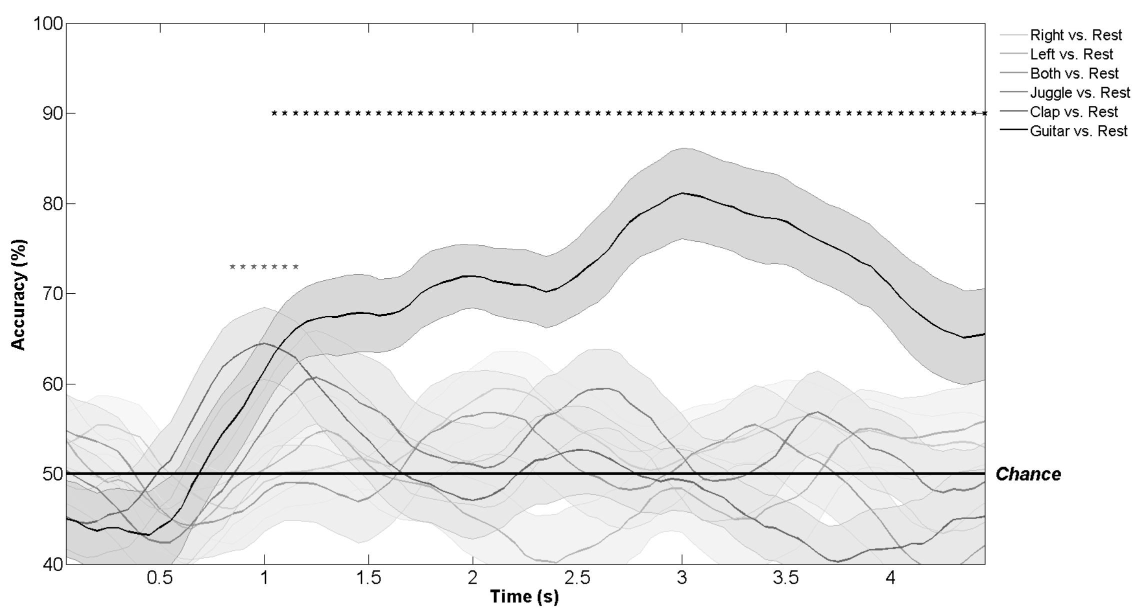

Figure 2. Single-trial analyses for a musician in Experiment 1 of Chapter 2.

Mean smoothed, cross-validated classification accuracy from the EEG single-trial analyses from an experienced guitar player who participated in Experiment 1

(Complexity). Time is measured relative to the offset of the instruction. Shaded regions depict ±1 standard error of the mean, and stars denote time-points with statistically reliable classification results.

2.3.2 Experiment 2: Familiarity

In terms of the single-trial analyses of the EEG data, there were no statistically reliable differences in accuracy for any of the imagined action versus rest comparisons, or for any group on any of the imagined action versus rest comparisons, $ps>.44$ (Table 4 and Appendix C). The main effect of group on accuracy approached statistical significance (p=.054), and this was driven by the relatively low overall classification accuracy of the hockey players (M=59.70%, SE=1.03%) compared to the control group (M=63.52%, SE=1.24%; pairwise p=.054). There were no statistically reliable differences in terms of the time at which maximum classification accuracy occurred for any imagined action or any group by imagined action type, ps>.64. There was also no statistically reliable difference in the number of trials included in any of the imagined action types or rest conditions on average or by group, ps>.41. Finally, the three groups did not differ in their self-reported vividness ratings of the imagined actions, p=.34, or in motor imagery ability as measured by the Movement Imagery Questionnaire (ps>.545; Table 3).

In the group spectral analyses of the EEG data (Figure 3), there were statistically reliable event-related desynchronizations for the familiar imagery versus rest comparisons for both the experienced pianists (ps<0.015) and the experienced hockey players (ps<0.019). Although the event-related desynchronizations were statistically reliable bilaterally (rather than unilaterally) and over a longer period for the pianists, the statistically reliable event-related desynchronizations were similar between the hockey players and pianists during imagery of familiar actions. Specifically, these event-related desynchronizations featured statistically reliable clusters in both the low-mu (8−10 Hz) and low-beta (13−19 Hz) bands. However, the pianists also had statistically reliable event-related desynchronizations for the hockey imagery (ps<.017) and the simple imagery (ps<0.017), and the hockey players had an event-related desynchronization that approached statistical significance (p=.036, two-tailed) for the simple imagery. Furthermore, the control group also produced statistically significant event-related desynchronizations for both the piano (*p*=.021) and hockey imagery (*p*=.002). There were no statistically reliable clusters in any of the other comparisons (*p*s>0.08). Thus, none of the imagined actions conferred a clear advantage in terms of sensorimotor rhythm detection for any group of participants, regardless of their familiarity (or lack thereof) with the imagined action.

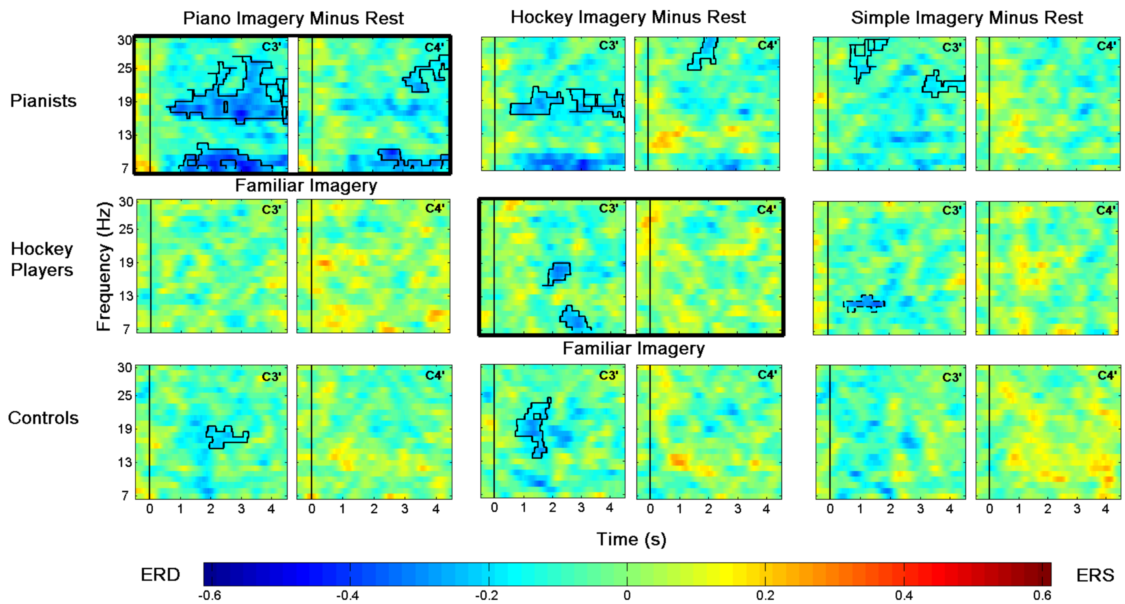

Figure 3. Outcomes of the group spectral analyses in Experiment 2 of Chapter 2.

Averaged, group time-frequency plots from the spectral analyses of the EEG data for Experiment 2 (Familiarity) by imagery versus rest comparison per familiarity group (*n*=16 per group). The range of power values (log ratio difference) that are plotted is ±0.6121. Statistically reliable clusters (*p*s<.021) are outlined with solid lines; dashed lines highlight a cluster with *p*=.036. Time is measured relative to the offset of the instruction.

2.3.3 Experiment 3: Complexity and familiarity

In terms of classification accuracy for the experiment only involving pianists, there was an advantage for the complex imagined action (Complex: *M*=69.60%, *SE*=2.03%) compared to the simple imagined action (Simple: *M*=66.34%, *SE*=1.96%; *t*(15)=-2.589, *p*=.021, *d*=0.65). Furthermore, more time-points were classified from rest for the complex imagery compared to the simple imagery, *Z*=-2.510, *p*=.009 (two-tailed), *r*=.63 (Simple: median of 9 time-points [range: 0-76]; Complex: median of 32 time-points [range: 0-74]). However, there was no difference between the number of pianists with statistically reliable imagery versus rest comparisons in the two complexity levels, Fisher's exact *p*=0.25. There also was no statistically reliable difference in terms of when the maximum classification accuracy occurred relative to the onset of the auditory cue, *p*=.72. The differences between the complexity conditions were not driven by a difference in the number of trials in either condition, *p*=.16. Notably, there was also no difference between the self-reported vividness of the imagined actions in Experiment 3 compared to Experiment 2, *p*=.10.

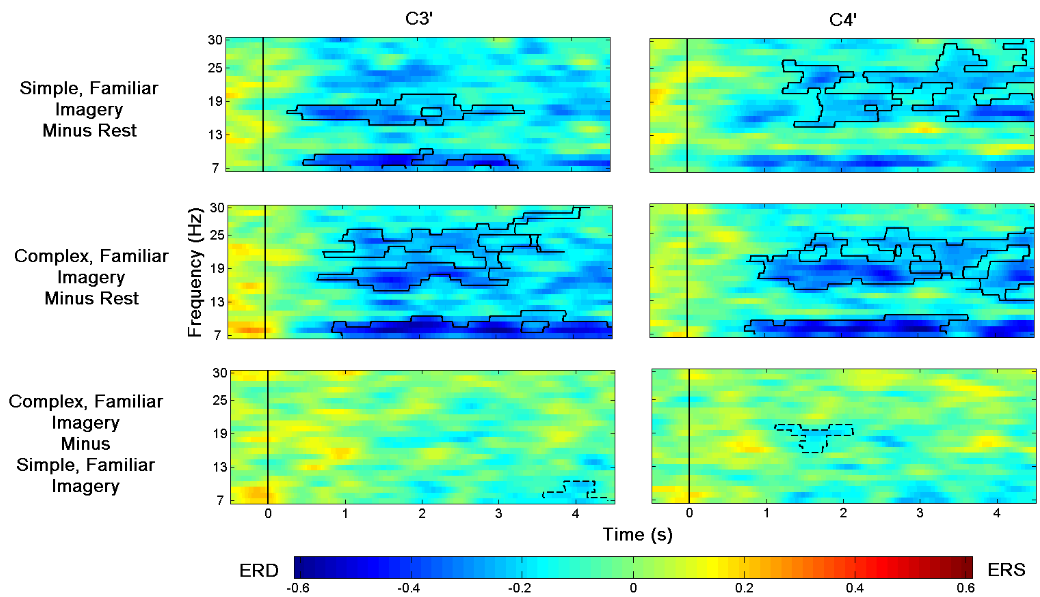

Figure 4. Outcomes of the group spectral analyses in Experiment 3 of Chapter 2.

Averaged, group (*n*=16) time-frequency plots from the spectral analyses of the EEG data from Experiment 3 (Complexity and Familiarity) by comparison. The range of power values (log ratio difference) that are plotted is ±0.6121. Statistically reliable clusters (*p*<.017) are outlined with solid lines; dashed lines highlight clusters with *p*=.044 (C3') and *p*=.038 (C4'). Time is measured relative to the offset of the instruction.

The results of the group spectral analyses are shown in Figure 4 for each comparison. Compared with rest, statistically reliable event-related desynchronizations (*p*s<.017) occurred in the low-mu and low-beta bands over the left hemisphere and in the low-, mid-, and high-beta bands over the right hemisphere for the simple imagery versus rest comparison. For the complex imagery versus rest comparison, a similar response was observed with the same time-course, although the event-related desynchronizations were statistically reliable over both hemispheres throughout the low-mu and the low- and mid-beta bands (*p*s<.011). In a comparison of the two imagery conditions, there was more of a desynchronization bilaterally for the complex imagery in the low-mu and low-beta bands that approached statistical significance (*p*s=.044 [C3'] and .038 [C4']).

As an exploratory *post-hoc* test, classification accuracy was compared for the sensorimotor rhythms generated when the pianists imagined playing a musical piece of their choice (Experiment 2) versus two specific musical pieces (Experiment 3). This analysis resulted in a significant effect of movement type, $F(15)=16.016$, $p=.001$, $\eta_p^2=.361$, that was driven by the lower classification accuracy for the piano imagery in Experiment 2 compared to the complex piano imagery in Experiment 3 ($p=.003$; Complex Musical Piece [Experiment 3]: *M*=69.60%, *SE*=2.03%; Musical Piece of Choice [Experiment 2]: *M*=63.31%, *SE*=1.49%; other pairwise *p*s>.06).

2.4 Discussion and conclusions

In this chapter, healthy volunteers, including experienced hockey players and pianists, imagined actions of varying complexity and familiarity in a series of motor imagery paradigms evaluated using EEG. The purpose of this work was to increase the likelihood that reliable and robust sensorimotor rhythms would be detected at the single-subject level. In future work, these manipulations will be applied to sensorimotor rhythm-based brain-computer interface paradigms intended to restore communication to patients with disorders of consciousness.

In Experiment 1, imagery of a range of bimanual sequences of actions ("complex imagery") resulted in sensorimotor rhythms that were classified from rest with similar accuracy as imagery of the simple hand squeezes typically used with sensorimotor rhythm-based brain-computer interfaces. There was a group trend that the complex actions were classified with higher accuracy than simple hand squeezes, although this result did not reach statistical significance ($p=.068$). Furthermore, there was an advantage for the complex actions in that the sensorimotor rhythms for these actions were classified from rest for a longer period than the simple actions. More participants also produced statistically reliable sensorimotor rhythms for at least one of the complex actions than for at least one of the simple actions. Overall, the findings of Experiment 1 align with the prediction that there would be an enhancement of the sensorimotor rhythm for complex imagery (Holper & Wolf, 2011; Kuhtz-Buschbeck *et al.*, 2003; Roosink & Zijdewind, 2010). In other words, imagined actions involving more than one body part and sequences of actions (complex motor imagery) may improve the detection of covert command following in future clinical work and do not necessarily result in less robust brain responses than conventional motor imagery.

Another interesting finding from Experiment 1 was the between- and within-subject variability for the various imagined actions. Nearly half of the sample produced a robust sensorimotor rhythm for at least one of the complex imagined actions, while less than 25% of the sample produced a robust sensorimotor rhythm for at least one of the simple imagined actions (Table 4). The latter observation is well-illustrated anecdotally by the classification results of two guitarists who participated in Experiment 1 (Figure 2). The guitarists imagined performing six different actions throughout their participation in this study, but both participants generated robust and sustained sensorimotor rhythms only when they imagined playing the guitar (defined as a complex action in this work). There was likely no advantage for the complex imagery at the group-level because most participants, like the guitarists, only produced significant responses for one or two of the complex imagined actions, rather than for all three of these actions. Accordingly, complex imagery catered to an individual's prior experience may enhance the neural correlates of imagined movement in some cases.

Experienced athletes and musicians were recruited for Experiments 2 and 3 to directly examine the influence of experience on the neural correlates of motor imagery. Somewhat surprisingly, there was no advantage for any of the imagined actions for any group in Experiment 2, regardless of their familiarity with the imagined actions (*e.g.*, pianists imagining playing piano, *etc.*). Compared to novices, experienced athletes and musicians differentially activate fewer regions of the brain when imagining actions involving the sport or instrument with which both groups have familiarity (Fourkas *et al.*, 2008; Lotze *et al.*, 2003; Olsson *et al.*, 2008; Wei & Luo, 2010). Although expert brain responses to familiar imagery are typically consistent within and across individuals (Langheim, Callicot, Mattay, Duyn, & Weinberger, 2002), these responses did not result in an enhancement of the sensorimotor rhythm in Experiment 2. Interestingly, however, there was an advantage for the classification of sensorimotor rhythms generated for specific, familiar actions (performance of two musical pieces) in Experiment 3. Classification accuracy was higher and robust for a longer period when the experienced pianists imagined playing a complex musical piece. Moreover, the imagery of particular musical pieces in Experiment 3 was associated with the largest and most sustained event-related desynchronizations of all the imagery conditions in this chapter (compare Figures 1, 3, and 4). Finally, classification accuracy was higher when pianists imagined playing the complex musical piece in Experiment 3 than when the same pianists imagined playing a musical piece of their choice in Experiment 2. It thus seems that imagery of a well-specified, complex, and familiar action leads to an advantage in sensorimotor rhythm detection.

Several factors likely contributed to the finding that the specific, complex, and familiar imagery from Experiment 3 resulted in the most robust sensorimotor rhythms of this chapter. Firstly, there was some variability between the two experiments involving imagined musical performance. In Experiment 2, participants were instructed to simply imagine playing the piano with both hands, rather than to imagine playing particular musical pieces as in Experiment 3. This variability likely resulted in less consistent and less robust brain responses over trials and between individuals, regardless of their familiarity with the piano. Notably, it is unlikely that the specificity of the instructions alone underlies the advantage of the Experiment 3 imagery, given that all the other imagery tasks in this work also involved specific instructions (*e.g.*, imagine squeezing your right hand, *etc.*). As an additional consideration, playing the piano involves temporally and spatially complex movements (Zatorre, Chen, & Penhune, 2007). Analogous finger-sequencing actions that do not require musical training are also associated with more robust brain responses than less temporally and spatially complex hand actions (Bengtsson, Ehrsson, Forssberg, & Ullén, 2004). It is accordingly possible that piano performance imagery was more conducive to an enhanced sensorimotor rhythm than the other imagined actions in this chapter. Although the imagery from

Experiment 3 is not appropriate for non-musicians, imagery involving music has been investigated in several previous brain-computer interface paradigms, including paradigms based upon the sensorimotor rhythm (*e.g.*, Curran *et al.*, 2004; Power, Kushki, & Chau, 2011; Schaefer, Farquhar, Blokland, Sadakata, & Desain, 2011). Indeed, the sensorimotor system supports music perception and performance, and musicians and non-musicians alike differentially activate the supplementary motor area and other premotor cortical areas when listening to complex rhythms and imagining familiar melodies (for a review, see Zatorre *et al.*, 2007). As a final possibility, imagery of actions that target other sensory modalities may further enhance the sensorimotor rhythm. An example of such imagery is imagining using a tool while imagining the noises that the tool makes (Felton, Wilson, Williams, & Garell, 2007; Wilson, Felton, Garell, Schalk, & Williams, 2006). Although the kinaesthetic (as opposed to visual) aspects of motor imagery correlate with sensorimotor rhythm magnitude (Neuper, Scherer, Reiner, & Pfurtscheller, 2005), a richer sensory representation of an imagined action may confer advantages in sensorimotor rhythm detection.

Altogether, this chapter provides three important findings regarding the roles of action familiarity and complexity in the EEG correlates of imagined movement. Firstly, imagery of complex, bimanual actions correlates with more robust brain responses in some cases, as anecdotally illustrated in Figure 2. Importantly, these modified imagery tasks do not necessarily impair performance compared to the hand-squeeze imagery typically used with sensorimotor rhythm-based brain-computer interfaces. Secondly, a familiar action may not always correlate with a more robust sensorimotor rhythm than other actions, but, thirdly and lastly, an action that is familiar, sufficiently complex, and well specified is likely to correlate with a more robust sensorimotor rhythm. Indeed, participants need prior experience with an action to reliably perform motor imagery of that action (Olsson & Nyberg, 2010). Similarly, brain responses to motor imagery are enhanced following overt practice of novel actions (Baeck *et al.*, 2012; Lacourse, Orr, Cramer, & Cohen, 2005). For these reasons, it is worthwhile to select an imagery task based on a person's skills and interests, regardless of the person's level of expertise with that action. Most importantly, the subtle but important changes in task instructions proposed here may provide benefits to those individuals who are unable to control a conventional sensorimotor rhythm-based brain-computer interface (*e.g.*, Figure 2), given the substantial variability between and within participants in previous work (Hammer *et al.*, 2011; Vidaurre & Blankertz, 2010).

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Chapter 3

3 Multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness

Gibson, R. M., Fernández-Espejo, D., Gonzalez-Lara, L., Owen, A. M., & Cruse, D. (2014). Multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness. *Frontiers in Human Neuroscience*, *8*, 950. http://dx.doi.org/10.3389/fnhum.2014.00950

3.1 Introduction

A key challenge in the differential diagnosis of disorders of consciousness is that these disorders arise from heterogeneous disruptions to brain structure and function. Patients may have traumatic or non-traumatic brain injuries, and comorbidity with other disorders and pathologies is common. Accordingly, there is often high variability between patients in the specific cognitive abilities that are preserved and disrupted. These differences are difficult to quantify because most patients cannot overtly respond (Monti, Pickard, & Owen, 2013; Rodriguez Moreno, Schiff, Giacino, Kalmar, & Hirsch, 2010). Furthermore, patients with disorders of consciousness are characteristically variable in their observable behaviour within relatively short time frames. It is not uncommon for a patient to exhibit different behaviours over the course of one day, although this variability typically subsides the longer the patient persists in the same conscious state and can be quantified with rigorous neuropsychological assessment (Cruse, Thibaut, *et al.*, 2013; Giacino *et al.*, 2002). To complement behavioural assessments, a patient's cognitive and perceptual abilities can be evaluated with neuroimaging (Gosseries, Di, Laureys, & Boly, 2014; Owen, 2013; Stender *et al.*, 2014). Unfortunately, however, some patients are ineligible for certain assessments. For example, metallic implants may be incompatible with MRI, and craniotomies can result in highly abnormal EEG recordings (Lee *et al.*, 2010). For these reasons, it is critical to utilize multiple assessment techniques (*e.g.*, behaviour, fMRI, EEG, *etc*.) with a range of cognitive and sensory tasks to obtain an accurate representation of a patient's abilities.

As previously discussed, the most widely adopted fMRI-based technique to assess covert cognition and awareness in patients with disorders of consciousness involves the neural correlates of mental imagery. Specifically, fMRI-based assessments often use both a motor imagery task ("imagine playing tennis") and a spatial navigation imagery task ("imagine visiting all the rooms in your house"; Owen *et al.*, 2006). These tasks engage distinct mental processes and are associated with similarly distinct brain responses. Specifically, the motor imagery task requires the participant to imagine swinging a tennis racket, while the spatial navigation task requires the participant to visualize the layout and contents of his or her home. Consequently, the motor task is associated with activation of the supplementary motor area, while the spatial navigation task is associated with activation of the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex. These regions of interest have been confirmed in several validation studies with healthy volunteers (Boly *et al.*, 2007; Fernández-Espejo, Norton, & Owen, 2014; Gabriel *et al.*, 2015; Naci, Cusack, Jia, & Owen, 2013; Owen & Coleman, 2007). In patient assessments, the reliability of the patient's brain response is determined by the patient's ability to sustain spatially appropriate activation throughout repeated, 30-second blocks of trials (Boly *et al.*, 2007; Fernández-Espejo *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006). Notably, this prolonged maintenance of a mental representation is the hallmark evidence for conscious processing in this paradigm (Dehaene & Naccache, 2001; Naccache, 2006).

EEG-based assessments of covert command following for patients with disorders of consciousness primarily rely upon motor imagery. The most successful EEG-based adaptations employ motor imagery conventionally used with brain-computer interfaces ("imagine squeezing your right hand into a fist"; Cruse *et al.*, 2011). The neural correlates of this task are reliable increases and decreases in EEG spectral power

(Vaughan *et al.*, 2006). Appropriate spectral changes are maximal over topographically appropriate areas of the motor cortex (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Pfurtscheller, Neuper, Brunner, & Lopes da Silva, 2005; Yuan, Perdoni, Yang, & He, 2011). For imagined squeezes of the right hand, appropriate responses are thus maximal over the left premotor cortex. Time-frequency analyses are typically employed to quantify power changes in the mu and beta frequency bands, which are classically defined as 7 to 12 Hz and 13 to 30 Hz, respectively (Neuper & Pfurtscheller, 2001; Pfurtscheller & Neuper, 1997). In patient assessments, permutation testing is recommended to determine the reliability of these responses (Billinger *et al.*, 2013; Cruse, Chennu, *et al.*, 2013; Goldfine *et al.*, 2013; Noirhomme *et al.*, 2014).

Although the EEG correlates of imagined hand squeezes are well documented, some healthy volunteers do not reliably exhibit these neural responses. In brain-computer interface applications, this phenomenon is known as brain-computer interface illiteracy, and it is estimated to account for about 10 to 30% of healthy volunteers who do not exhibit reliable EEG responses during conventional motor imagery (Hammer *et al.*, 2011; Vidaurre & Blankertz, 2010). About 15% of patients diagnosed as being in a Vegetative State reliably regulate their brain responses to command (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016). Given this small portion of eligible patients, a desirable improvement in EEG-based assessments of covert command following is a reduction in the likelihood of brain-computer interface illiteracy. Accordingly, the patients in this chapter were also asked to perform motor imagery of an action identified as familiar to them by their caregivers. This task was motivated by the results of previous work with non-brain-injured volunteers, including those described in Chapter 2 (Curran *et al.*, 2004; Curran & Stokes, 2003; Gibson, Chennu, Owen, & Cruse, 2014; Scherer *et al.*, 2015). Briefly, experienced athletes and musicians produce more focused and reliable patterns of brain activation when they imagine actions involving the sport or instrument with which they have experience (Lotze, Scheler, Tan, Braun, & Birbaumer, 2003; Wei & Luo, 2010). It was accordingly expected that familiar imagery would result in more robust brain responses from patients and thus reduce the likelihood that patients with the ability to covertly follow commands would not be identified in the EEG-based assessment.

When a familiar action could not be identified, patients were asked to imagine dialling on a telephone. This action was selected because motor imagery of finger sequencing actions correlates with robust responses from cortical motor areas and enhanced motor evoked potentials relative to simpler hand actions (Bengtsson, Ehrsson, Forssberg, & Ullén, 2004; Roosink & Zijdewind, 2010). The EEG correlates of familiar motor imagery were quantified and evaluated in the same way as the EEG correlates of conventional motor imagery.

In this chapter, a small group of patients with disorders of consciousness underwent neuropsychological evaluations and fMRI- and EEG-based assessments of covert command following. Behavioural assessments were performed using the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005). In the fMRI assesment, patients were asked to perform the motor imagery and spatial navigation imagery tasks previously discussed (Boly *et al.*, 2007; Owen *et al.*, 2006). In the EEG assesment, patients were asked to imagine squeezing their right-hand (conventional motor imagery; Cruse *et al.*, 2011) and an action with which they had experience prior to their brain injury (familiar motor imagery). In light of the findings of Chapter 2, it was expected that familiar motor imagery would result in more reliable EEG responses than conventional motor imagery (Gibson *et al.*, 2014). Furthermore, it was predicted that these distinct neural correlates of covert command following would provide corroborative evidence for each patient's residual abilities.

3.2 Materials and methods

3.2.1 Participants

An initial convenience sample of 14 patients with acquired brain injuries and disorders of consciousness diagnoses ranging from the Vegetative State to the Minimally Conscious State *Plus* were recruited for the EEG and fMRI tasks. Substitute decision makers provided written, informed consent for the patients. Ethical approval was obtained from Western University's Health Sciences Research Ethics Board. Three patients were excluded from the sample because they were ineligible for the fMRI assessment; two patients were excluded because they had craniotomies that resulted in poor quality EEG data (Lee *et al.*, 2010); and three other patients were excluded due to excessive movement artefacts. The remaining sample of six patients comprised three patients in a Vegetative State and three patients in a Minimally Conscious State. Five patients (Patients 2-6) completed the fMRI and EEG experimental procedures in the same week with one to three days between sessions, and one patient (Patient 1) completed the fMRI experimental procedure seven months prior to the EEG experimental procedure. In the latter case (Patient 1), the patient's ability to follow commands in neuroimaging-based assessments has been previously documented using the same fMRI mental imagery described here (Fernández-Espejo & Owen, 2013), an fMRI-based attentional paradigm (Naci & Owen, 2013), and an EEG attempted movement paradigm (Cruse *et al.*, 2012). Demographic and clinical data for the final sample of patients is included in Table 5.

Table 5. Demographic and clinical data for the patients discussed in Chapter 3.

ID	**Sex/ Age (years)**	**Interval since Ictus (years)**	**Aetiology**	**Diagnosis**	**CRS-R Subscale Scores[a]**					
					Aud	**Vis**	**Mot**	**Oro**	**Com**	**Aro**
1	M/38	13 (fMRI) 13.6 (EEG)	*Traumatic* Traumatic brain injury secondary to a motor vehicle collision	Vegetative State	1	1	2	1	0	2
2	F/20	6	*Non-Traumatic* Undiagnosed progressive neuromuscular deterioration	Vegetative State	2	1	2	1	0	2
3	M/27	4	*Non-Traumatic* Anoxic brain injury secondary to cardiac arrest	Minimally Conscious State *Plus*[b]	3	3	2	2	0	3
4	F/46	20	*Non-Traumatic* Hypoxic brain injury due to near-drowning	Minimally Conscious State *Minus*	2	3	2	1	0	2
5	M/57	4	*Non-Traumatic* Diffuse anoxic brain injury secondary to cardiac arrest	Vegetative State	1	0	2	1	0	2
6	F/35	2	*Non-Traumatic* Anoxic brain injury secondary to cardiac arrest	Vegetative State	1	0	2	1	0	1

Notes. fMRI=functional Magnetic Resonance Imaging; EEG=electroencephalography; CRS-R=Coma Recovery Scaled-Revised; Aud=auditory; Vis=visual; Mot=motor; Oro=oromotor/verbal; Com=communication; Aro=arousal; M=male; F=female.

[a]Highest CRS-R score recorded by the research team until the time of assessment. For Patients 2-6, this period was three to nine months (see text for details). For Patient 1, this period was 24 months (21 evaluations).

[b]Patient 3 generated reproducible movements to verbal commands on the auditory sub-scale of the CRS-R during each evaluation.

3.2.2 Imagery tasks

During the fMRI testing sessions, patients were asked to perform alternating sessions of repeated rest-imagery cycles. Each period of imagery or rest lasted for 30 seconds, and each patient completed five cycles for both imagery tasks. In the motor imagery task, participants were instructed to imagine swinging their right arm to firmly hit a tennis ball, as if competing in a tennis match. In the spatial navigation task, the patients were instructed to imagine moving from room to room in their homes whilst visualising all the objects they would encounter. The experimental procedure has been reported in previous work (Boly *et al.*, 2007; Fernández-Espejo *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006).

For the EEG task, the procedure was similar to that reported in (Cruse *et al.*, 2012; Gibson *et al.*, 2014). Specifically, every trial began with one of three instructions: 'Imagine squeezing your right hand', 'Imagine dialling 9-1-1' (or a custom action, detailed in Table 6), and 'Now, please just relax'. All instructions were 3 seconds in length and were followed by 2 to 5 seconds of silence. The silent interval was randomly selected from a uniform distribution on each trial, and the instructions were presented by earphone. The task was completed in blocks of 48 trials (16 trials per instruction) presented in a pseudorandom order such that no more than three instructions of the same type were consecutively presented. Each patient completed four or five blocks during the assessment, for a total of 192 (four blocks) or 240 (five blocks) trials, with short breaks between each block.

Table 6. Familiar motor imagery tasks for the patients discussed in Chapter 3.

Patient ID	**Familiar Imagery Task**
1	Make a tennis serve
2	Dial 9-1-1
3	Lift a weight
4	Play a scale on the piano
5	Kick a soccer ball
6	Dial 9-1-1

3.2.3 fMRI data acquisition and analysis

fMRI data were acquired in a 3 Tesla Siemens scanner (Magnetom Trio Tim, Siemens, Germany) with a Siemens 32-channel head-coil (Patients 2, 3, and 6) or a Siemens 12-channel head-coil (Patients 1, 4, and 5) at the Centre for Functional and Metabolic Mapping (Robarts Research Institute, Western University, Canada). Head-coils were chosen for patient comfort. The MRI protocol included a single session of 165 volumes of 36 axial slices each covering the whole brain using echo-planar images (repetition time=2,000 ms, echo time=30 ms, matrix size=70×70, slice thickness=3 mm, in-plane resolution=3×3 mm, flip angle=78°). High-resolution T1-weighted three-dimensional magnetization-prepared rapid gradient-echo images were acquired in the same session (repetition time=2,300 ms, echo time=2.98 ms, inversion time=900, matrix size=256×240, voxel size=1 mm^3, flip angle=9°). The task instructions and cues were presented using E-Prime® 2.0 running on Windows XP and an MRI-compatible high-quality digital sound system incorporating noise-attenuating headphones (Silent Scan™, Avotec Inc.).

The fMRI data were pre-processed and analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Data were first manually reoriented into the anterior commissure/posterior commissure plane. Spatial pre-processing included: realignment to correct for motion; co-registration between the structural and functional data sets; and smoothing with an 8-mm full width at half maximum Gaussian kernel. Single-subject fixed-effect analyses were then performed for each patient. The analysis was based on the general linear model using the canonical hemodynamic response function (Friston *et al.*, 1995). Each scan was modelled as mental imagery (*i.e.,* motor imagery or spatial navigation) or rest. Movement parameters calculated from the realignment step were also included as covariates of non-interest. Additionally, repetition times with levels of motion above 2 mm and 0.035 radians were discarded. High-pass filtering using a cut-off period of 128 seconds was implemented to remove slow-signal drifts from the time series. Linear contrasts were used to obtain subject-specific estimates of the effects of interest.

In healthy volunteers, spatial navigation imagery is typically associated with strong and reliable activity in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex, while tennis imagery elicits activity in the supplementary motor area (Boly *et al.*, 2007; Fernández-Espejo *et al.*, 2014). For reference, single-subject activation in a prior study of 14 healthy young adults is depicted in Figure 5 (Fernández-Espejo *et al.*, 2014). In the current study involving patients with disorders of consciousness, a voxel level, family-wise error, whole-brain statistical threshold of $p<0.05$ was used. Given the strong anatomical *a priori* hypotheses, however, the statistical threshold was reduced to an uncorrected $p<0.001$ when activation was not detected at the more conservative threshold (Fernández-Espejo *et al.*, 2010; Friston, Holmes, Poline, Price, & Frith, 1996).

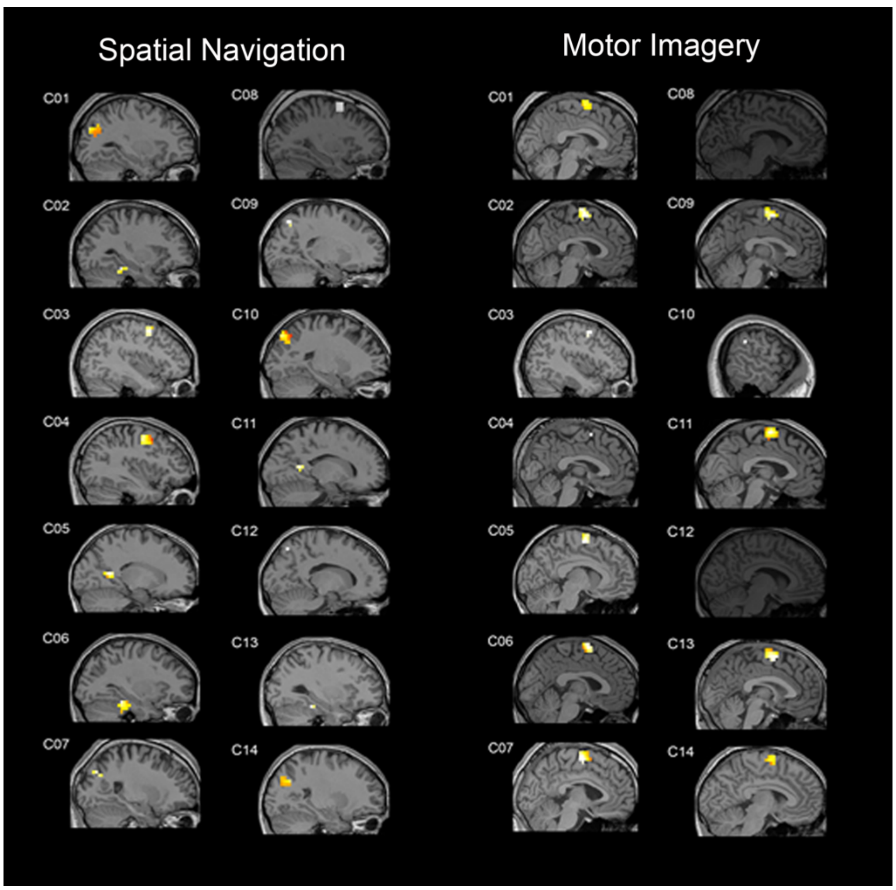

Figure 5. Activation from healthy young adults during spatial navigation and tennis motor imagery (Fernández-Espejo *et al.*, 2014).

The figure depicts single-subject blood-oxygen-level dependent responses from 14 healthy volunteers during mental imagery. The participants completed the same two mental imagery tasks (spatial navigation and tennis motor imagery) as in the current work. All participants were scanned using the same 3 Tesla Siemens scanner, and their fMRI data were processed using the same pipeline and analysis procedure as reported in this chapter. In the figure, the region of interest showing highest consistency across scanning sessions in the imagery versus rest contrast is displayed with a family-wise error-corrected statistical threshold of $p<0.05$. No scaling for the inset statistical maps was provided in the original publication and is accordingly not included in this thesis. All participants aside from C03, C08, C10, and C12 reliably activated the supplementary motor area for tennis imagery. Participants C03 and C10 reliably activated other anatomically appropriate areas for tennis imagery (dorsal premotor cortex and inferior parietal lobule), while Participants C08 and C12 failed to show any appropriate activation for tennis imagery. For spatial navigation, the following regions were reliably activated: occipito-parietal junction (C01, C07 C14); parahippocampal cortex (C02, C06, C13); dorsal premotor cortex (C03, C04, C08); retrosplenial cortex (C05, C11); and precuneus (C09, C10, C12). This image is reproduced in a slightly modified version with the permission of D. Fernández-Espejo from the original open-source publication (Fernández-Espejo *et al.*, 2014).

3.2.4 EEG data acquisition and analysis

The EEG acquisition and pre-processing protocol was the same as that reported in Chapter 2 (Gibson *et al.*, 2014). Briefly, the EEG data were recorded using the g.Gamma active electrode system with a four-channel montage housed in an electrode cap (g.tec Medical Engineering GmbH, Austria). The electrodes were placed at sites CP3, FC3, CP4, and FC4, and the EEG signals were acquired using a g.USBamp amplifier. Stimuli presentation and physiological data recordings were performed using a Simulink® model in Matlab (Mathworks, Inc., Natick, MA). Online, the EEG data were filtered from 0.5 to 60 Hz with a 60 Hz notch filter. The recordings were referenced to the right earlobe with a forehead (Fpz) ground. The data were sampled at 600 Hz with impedances below 5 kΩ at the beginning of the EEG recording.

Offline data processing was conducted with EEGLAB (Delorme & Makeig, 2004). The EEG data were down-sampled to 100 Hz, filtered between 0.5 and 40 Hz, and segmented into 5-s epochs time-locked to the onset of the auditory cue. Trials containing physiological artefacts were identified by visual inspection and removed. After artefact rejection, the median number of trials included in each imagery and rest condition per patient was: 43 for the hand squeeze (range=29−57); 45 for the custom action (range=32−57); and 44 for rest (range=27−58). Finally, the EEG data were re-referenced offline to form two bipolar channels (FC3−CP3, FC4−CP4) that are subsequently identified as C3' and C4', respectively.

The EEG data were analysed from 7 to 30 Hz using the same spectral analysis procedure reported in previous work and Chapter 2 (Cruse *et al.*, 2012; Gibson *et al.*, 2014). In Figure 6, patterns of spectral changes from a sample of six healthy young adults using the same task and analysis procedure are presented (Cruse *et al.*, 2012). For each time-point at C3' and C4', spectral power estimates were calculated using a 1-second Hanning window time-frequency transformation via the 'ft_freqstatistics' function from the open-source Matlab toolbox, FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011). The time-frequency data at both electrodes were then compared between motor imagery and rest using cluster-based permutation testing (Cruse *et al.*, 2012; Gibson *et al.*, 2014; Maris & Oostenveld, 2007). For the cluster-based testing, the time-frequency data for each imagery condition and rest were log-transformed and then compared at each data point using paired-samples t tests. All significant data points ($p<0.025$) were then arranged into clusters based on their temporal and spectral proximity to each other, and the t values were summed for each cluster. A Monte Carlo randomization test that controlled for family-wise error was used to determine the significance value for each cluster. In the randomization test, the condition labels were permuted, and the clustering procedure was repeated 1,000 times. The clusters from these 1,000 repetitions were used to form a distribution, and this distribution was then used to test the null hypothesis that the original summed t value occurred by chance.

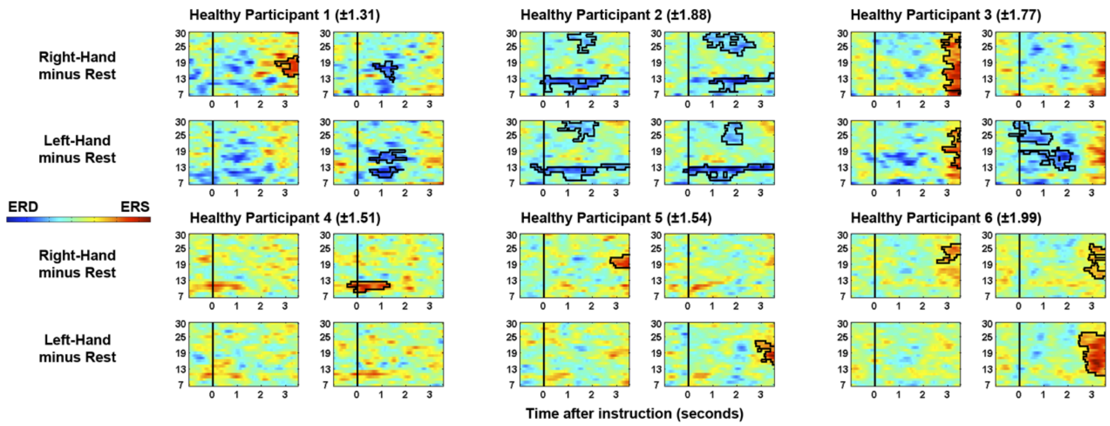

Figure 6. EEG responses from healthy young adults during conventional motor imagery (Cruse *et al.*, 2012).

The figure depicts event-related desynchronizations and event-related synchronizations over left and right motor cortex in a sample of six healthy young adults. The participants completed the same conventional EEG motor imagery task as in the current work (right hand motor imagery) and an additional task of left hand motor imagery, as indicated. The ranges of log power values that are plotted in each spectrogram are indicated in parentheses at the top of each plot. This figure is reproduced with the permission of D. Cruse from the original open-source publication (Cruse *et al.*, 2012).

3.3 Results

Figure 7 provides a summary of the results from the behavioural, EEG, and fMRI assessments for each patient. Patient 1 was diagnosed as being in a Vegetative State from 21 evaluations with the Coma Recovery Scale conducted in the 24 months prior to the fMRI/EEG assessments (highest score=7, range=4−7). In the fMRI study, this patient produced reliable and appropriate activation in both the spatial navigation and motor imagery tasks (occipito-parietal junction and supplementary motor area respectively, family-wise error $p<0.05$). In the EEG task, Patient 1 also produced a contralateral event-related desynchronization in the mu frequency band (9−13 Hz) for the conventional imagery ($p=0.018$). Patient 2's highest score on the Coma Recovery Scale was 8 (range: 4−8, period: five assessments in four months), leading to a diagnosis of Vegetative State. Patient 2 did not produce reliable activation in the fMRI tasks or reliable spectral changes in the EEG tasks. Patient 3 scored in the Minimally Conscious State *Plus* range (highest score=13, range=11−13, period: four assessments in four months). This patient did not produce significant activation during the fMRI tasks. However, he did produce appropriate, reliable spectral changes during the conventional EEG motor imagery task (contralateral event-related desynchronization, 7−13 Hz, $p=0.004$). Patient 4 was diagnosed as being in a Minimally Conscious State *Minus* (highest score=10, range=8−10, period: three assessments in nine months). Although this patient showed no activation at the conservative threshold (family-wise error $p<0.05$), she produced reliable, appropriate activation during the fMRI spatial navigation task in the bilateral occipito-parietal junction (uncorrected $p<0.001$). However, Patient 4 did not produce reliable, appropriate activation for the fMRI motor imagery task, or the EEG motor imagery tasks. Patient 5 scored in the Vegetative State range (highest score=6, range=3−6, period: four assessments in five months) and did not produce reliable responses for any of the fMRI or EEG assessments. Finally, Patient 6 also scored in the Vegetative State range (highest score=5, range=3−5, period: four assessments in three months). As with Patient 4, reliable, appropriate activation was detected during the spatial navigation fMRI task (right parahippocampal gyrus and right premotor cortex, family-wise error $p<0.05$). However, this patient did not produce reliable activation for the fMRI motor imagery task, or the EEG motor imagery tasks.

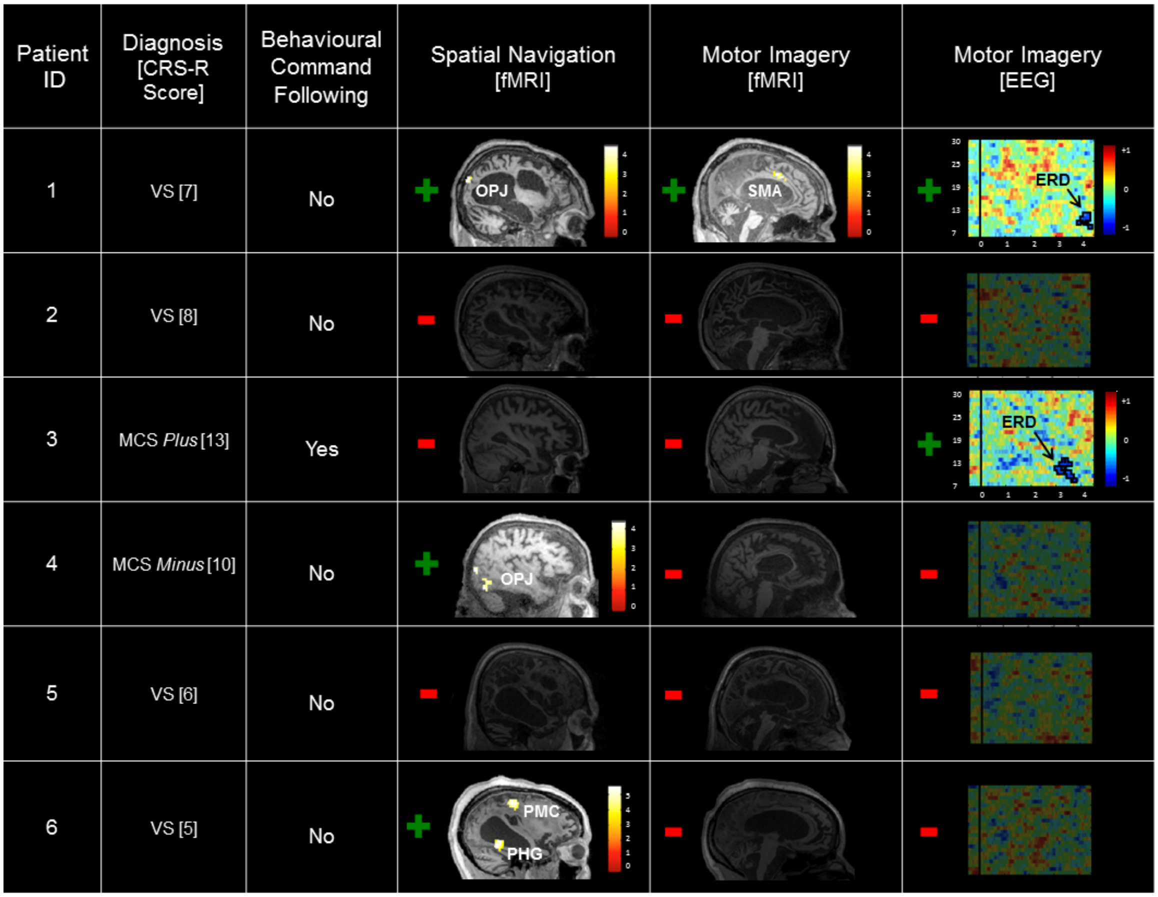

Figure 7. Summary of the patient outcomes in Chapter 3.

CRS-R=Coma Recovery Scale-Revised; fMRI=functional magnetic resonance imaging; EEG=electroencephalography; VS=Vegetative State; MCS=Minimally Conscious State; OPJ=occipito-parietal junction; SMA=supplementary motor area; PMC=premotor cortex; PHG=parahippocampal gyrus; ERD=event-related desynchronization. Significant task-related fMRI activation is labelled by region. Scales depicting the statistical maps (*t* values) are inset. Results are shown at uncorrected $p<0.001$ and rendered on each patient's T1 MRI image. Spectrograms of the log ratio differences in EEG power between conventional motor imagery and rest are shown for the left (contralateral) hemisphere. The vertical axis depicts the frequency of the EEG signal (7−30 Hz), and the horizontal axis depicts time (seconds) relative to instruction onset. The inset colour scale depicts the log ratio power values of the z-axis with significant clusters outlined in black (Patient 1, p=0.018; Patient 3, p=0.004).

To complement the experimental neuroimaging-based assessments, clinical radiologists (authors BYK and DHL in the published version of this chapter) provided assessments of the available clinical structural images of each patient's brain. The radiologists were blinded to all aspects of the patient's identities, diagnoses, and experimental outcomes. The time of the clinical assessments varied for each patient, but all scans had been conducted near the time the patients were admitted following their brain injuries for Patients 1 and 5. More recent clinical assessments were available for the remaining patients, although no clinical structural brain images were available for Patient 4. The radiological reports are summarized in Table 7. The only finding involving a brain region of interest in these assessments was low signal change in the bilateral pre- and post-central gyri of Patient 6. This area is a region of interest in the fMRI-based motor imagery task.

Table 7. Summary of the radiological evaluations of available clinical structural brain images for the patients in Chapter 3.

Patient ID	Radiological Findings
1	Moderately severe contralateral shift to the midline Effaced subarachnoid space and convexity sulci
2	Generalised brain edema Decreased grey and white matter differentiation No sign of hematomas or contusions
3	Diffuse progressive atrophic change Volume loss with severe ventricular dilation
4	Clinical images unavailable for assessment
5	Areas of signal change within the caudate nuclei and putamen Some attenuation of the distal arterial branches No vascular irregularity in the proximal vessels
6	Decreased signal and restricted diffusion in cerebral white matter Low signal within white matter of the pre- and post-central gyri bilaterally No evidence of bleed

In summary, six patients were evaluated using a standard clinical behavioural assessment, the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005), two fMRI-based imagery tasks (Boly *et al.*, 2007; Owen *et al.*, 2006), and two EEG-based motor imagery tasks (Cruse *et al.*, 2011; Gibson *et al.*, 2014). Patient 1 (Vegetative State) was unable to follow commands behaviourally, but exhibited covert command following in both the fMRI- and EEG-based tasks. Two patients (Patient 4 [Minimally Conscious State *Minus*] and Patient 6 [Vegetative State]) also showed no signs of behavioural command following, but exhibited covert command following in the spatial navigation fMRI task. Patient 3 (Minimally Conscious State *Plus*) followed commands behaviourally and covertly in the conventional motor imagery EEG task. Finally, Patients 2 and 5 (both Vegetative State) did not follow commands in either the behavioural, fMRI-, or EEG-based assessments.

3.4 Discussion and conclusions

Functional neuroimaging methods for the detection of covert command following can improve diagnostic and prognostic accuracy in disorders of consciousness (Owen, 2013). Due to the heterogeneity of aetiology and pathology in this patient group, however, multiple imaging techniques and functional tasks are necessary to accurately identify a covert ability to follow commands. In this chapter, three patients who were unable to follow commands with their behaviour exhibited appropriate and statistically reliable signs of covert command following. Furthermore, two of these patients (Patients 1 and 6) were repeatedly diagnosed as being in a Vegetative State. These findings thus add to the growing body of evidence that some patients with severe brain injuries have cognitive abilities that are not necessarily evident from their external behaviour (Kondziella *et al.*, 2016; Owen, 2013).

One patient diagnosed as being in a Vegetative State (Patient 1) exhibited covert command following during both the fMRI- and EEG-based motor imagery tasks—*i.e.,* “imagine playing tennis” in the fMRI-based assessment, and “imagine squeezing your right-hand” in the EEG-based assessment. The covert awareness of this patient has been previously reported in other fMRI and EEG tasks (Cruse *et al.*, 2012; Fernández-Espejo & Owen, 2013; Naci & Owen, 2013). Indeed, across all published studies, this patient demonstrated his covert awareness with three separate fMRI tasks and two EEG tasks, thus providing perhaps unequivocal evidence that he was aware. Although internally consistent, these findings conflict with the outcomes of repeated clinical evaluations throughout the 12 years in which the patient survived following his injury.

Two patients (Patient 4 [Minimally Conscious State *Minus*] and Patient 6 [Vegetative State]) only followed commands during the spatial navigation fMRI imagery task. The absence of statistically reliable results in the EEG tasks for these patients is consistent with the absence of reliable activation during the fMRI ‘tennis’ task in the same patients, as both tasks require brain responses that correlate with motor imagery. From their radiological findings (Table 7), Patient 6 (Vegetative State) presented with specific damage to motor areas as evident from scattered areas of low fluid attenuation inversion recovery signal and high white matter signal in the posterior precentral gyrus. Patient 1, on the other hand—also Vegetative State but, unlike Patient 6, capable of successful performance in the motor imagery tasks—showed no apparent damage to motor areas bilaterally. Together, these findings suggest that the absence of reliable motor imagery responses may be a result of a specific impairment in motor planning, or at least in the detectability of EEG/fMRI responses from brain areas that correlate with motor function.

Patient 4 (Minimally Conscious State *Minus*) also followed commands only during spatial navigation. Unlike Patient 6, however, Patient 4 did not present with any damage to cortical motor areas. Notably, this patient was tested about twenty years after her injury. It is possible that functional reorganization in motor areas occurred in this time, although it is unclear why such functional reorganization would have occurred in brain areas that correlate with motor imagery and not spatial navigation imagery. Nevertheless, the results of Patients 4 and 6 together emphasize the importance of a battery of assessments to accurately characterise a given patient's abilities. Indeed, if motor imagery were the only option provided to Patients 4 and 6, their covert awareness may have never been elucidated.

Patient 3 (Minimally Conscious State *Plus*) could follow simple behavioural commands and exhibited covert command following in the EEG conventional motor imagery task. However, this patient did not yield positive results in either of the fMRI-based assessments. While the presence of awareness was never in question for this patient due to his behavioural diagnosis of Minimally Conscious State *Plus*, his divergent fMRI and EEG results again highlight the importance of multiple modalities and tasks in the assessment of patients with disorders of consciousness. Indeed, the fMRI and EEG assessments were performed on different days and at various times of the day, thereby increasing the patient's opportunities to demonstrate his command following capacities. Moreover, varying levels of arousal and awareness are defining traits of patients in a Minimally Conscious State (Giacino *et al.*, 2002) and may have contributed to the divergence between behaviour and fMRI in this case.

Patients 2 and 5 (both Vegetative State) did not demonstrate command following in any of the fMRI- or EEG-based assessments. These results mirror the outcomes of their behavioural evaluations. Indeed, patients in a Vegetative State completely lack voluntary behaviour, and very few patients diagnosed as being in a Vegetative State possess covert awareness and cognition (Di Perri *et al.*, 2016; Kondziella *et al.*, 2016; Schiff & Fins, 2016). It is accordingly plausible (and quite probable) that the converging results of the assessments of Patients 2 and 5 accurately represent the abilities of these patients. Nevertheless, and as has been discussed at length elsewhere, null neuroimaging findings from patients with disorders of consciousness cannot be interpreted as a lack of awareness *per se* (Laureys & Boly, 2007; Owen *et al.*, 2006). Indeed, false negatives may occur due to fatigue, lack of understanding, or insufficient cognitive resources. In the absence of self-report, it is difficult to distinguish negative findings that arise from a lack of ability from those that arise due to an intention not to perform the task. Healthy volunteers and patients with brain injuries may elect not to engage in a volitional mental process, and false negatives occur in neuroimaging studies of healthy volunteers, especially at the single-subject level (*e.g.,* Cruse *et al.*, 2011; Fernández-Espejo *et al.*, 2014; Naci, Cusack, Jia, & Owen, 2013). Although multiple assessments can provide a more thorough characterisation of a patient's abilities, these approaches do not eliminate the possibility of attribution errors.

This chapter also included an exploratory secondary EEG motor imagery task. All patients were asked to perform two types of motor imagery during the EEG task: 1) imagined squeezes of their right-hands, in line with conventional motor imagery EEG tasks (Cruse *et al.*, 2011, 2012; Pfurtscheller & Neuper, 1997); and 2) imagined familiar actions that were selected in consultation with their caregivers. Unfortunately, there were no positive results for any patient during the familiar EEG motor imagery task, even though two patients demonstrated positive results during the conventional EEG motor imagery task. One potential explanation for the lower sensitivity of the familiar imagery in this chapter is that familiar imagery resulted in brain responses that were not detected with the present EEG acquisition protocol. For example, imagined familiar actions may have involved memories or emotions to a greater extent than hand squeezes. Kinaesthetic motor imagery is associated with more robust EEG correlates of imagined movement than visual motor imagery (Neuper, Scherer, Reiner, & Pfurtscheller, 2005). Accordingly, the patients may have engaged in more visual imagery during the familiar task, and consequently produced brain responses that were not easily detected with the current experimental set-up. Fortunately, both patients (Patients 1 and 3) who exhibited reliable EEG responses to conventional motor imagery produced sensorimotor rhythms that are consistent with previous studies of healthy individuals (Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller & Neuper, 1997). This finding is reassuring for further investigations of the EEG correlates of motor imagery in patients with disorders of consciousness.

As a final consideration, attempts have been made to develop an EEG-based assessment of covert command following using spatial navigation (Cabrera & Dremstrup, 2008; Curran *et al.*, 2004; Goldfine, Victor, Conte, Bardin, & Schiff, 2011). These attempts employed an identical imagery task as the fMRI-based equivalent (Boly *et al.*, 2007; Owen *et al.*, 2006). Notably, spatial navigation imagery was associated with better classification accuracy than motor imagery in one EEG study of healthy volunteers (Curran *et al.*, 2004), and modest improvements in classification accuracy were obtained with optimized machine learning techniques (Cabrera & Dremstrup, 2008). In terms of electrophysiological correlates, spatial navigation imagery corresponds with enhanced theta oscillatory activity in the hippocampus and related brain structures in the medial temporal lobe (Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; see also Maguire, Frackowiak, & Frith, 1997). Unfortunately, these signals are not easily detected at the scalp, and no consistent EEG-based correlate of spatial navigation was identified in any of the studies that employed acquisition protocols suitable for future use at the bedside (Cabrera & Dremstrup, 2008; Curran *et al.*, 2004; Goldfine *et al.*, 2011). Similarly, the only reported validation of an EEG-based spatial navigation task involving patients with disorders of consciousness rendered inconclusive results (Goldfine *et al.*, 2011). Accordingly, an EEG-based assessment of spatial navigation imagery was not included in this thesis because there is no reliable EEG correlate of this mental task.

In summary, covert signs of awareness can improve diagnostic and prognostic accuracy in patients with disorders of consciousness (Owen, 2008). The current findings demonstrate that a range of tasks and neuroimaging modalities are required to accurately characterise residual cognition in patients with disorders of consciousness. Indeed, two patients failed to follow commands in motor imagery tasks, but produced appropriate activation in a spatial navigation task. In these cases, the patients' specific patterns of brain damage may have disproportionately impaired some cognitive abilities, or made their neural markers more difficult to detect. An effective battery of assessments for patients with disorders of consciousness should therefore include a variety of tasks that probe a range of cognitive abilities supported by spatially-distinct brain regions and indexed by multiple neural signatures, including EEG oscillations, event-related potentials, and fMRI-detected hemodynamic responses. Indeed, five patients were excluded from the current study because they did not qualify for evaluations with one of the two neuroimaging techniques. While no neuroimaging-based task is likely to be 100% sensitive, the implementation of a battery of assessments alongside standardized behavioural evaluations will go a long way to address the currently low rate of diagnostic accuracy for patients with disorders of consciousness (Childs, Mercer, & Childs, 1993; Schnakers *et al.*, 2009).

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Chapter 4

4 Somatosensory attention identifies both overt and covert awareness in disorders of consciousness

A version of this chapter has been published elsewhere (citation below) and is reproduced here with permission from the publisher, John Wiley and Sons (Appendix B).

Gibson, R. M., Chennu, S., Fernández-Espejo, D., Naci, L., Owen, A. M., & Cruse, D. (2016). Somatosensory attention identifies both overt and covert awareness in disorders of consciousness. *Annals of Neurology*, 80(3), 412–423.
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4.1 Introduction

To facilitate the differential diagnosis of disorders of consciousness, researchers have developed assessments of brain function to describe a patient's abilities within a hierarchy of increasingly complex information processing. For example, an fMRI-based technique was developed to characterise the speech processing abilities of patients with disorders of consciousness (Coleman *et al.*, 2009). This approach distinguished between low-level auditory processing, speech-specific perceptual processing, and semantic processing. While the level of auditory processing had a high correspondence with subsequent behavioural recovery, it did not provide diagnostic information—*i.e.*, some patients in a Vegetative State and other patients in a Minimally Conscious State performed at each level of the hierarchy (Coleman *et al.*, 2009). A similar technique was developed using EEG, with levels ranging from the discrimination of sound versus silence to semantic speech perception (Beukema *et al.*, 2016; Cruse *et al.*, 2014). As in the fMRI approach, however, some patients in a Vegetative State and other patients in a Minimally Conscious State performed at all levels of the hierarchy (Beukema *et al.*, 2016). Investigations of attentional processing have rendered similar findings; while some investigators reported that only patients in a Minimally Conscious State produced markers of higher-order attentional information processing (Bekinschtein *et al.*, 2009; Chennu *et al.*, 2013; Faugeras *et al.*, 2012; Lew *et al.*, 2003), others did not (Fischer, Luaute, & Morlet, 2010; Kotchoubey *et al.*, 2005; Steppacher *et al.*, 2013). Although neuroimaging-based assessments of patients with disorders of consciousness can complement behavioural evaluations, improvements are needed to ensure that a patient's abilities are accurately represented when there are discrepancies between behavioural and neural profiles.

The inconsistent correspondence between diagnosis and the presence or absence of neural markers of higher-order information processing in previous work may be due to misdiagnoses of covert command following. Indeed, only one of these investigations identified patients with covert command following abilities (Chennu *et al.*, 2013). Up to 15% of patients diagnosed as being in a Vegetative State may have the ability to covertly follow commands (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016), and it would be useful to characterise the cognitive abilities of such patients. Additionally, most previous approaches to cognitive assessments of patients with disorders of consciousness rely on auditory information (*c.f.* Monti *et al.*, 2013). While visual stimuli are impractical given that many patients with disorders of consciousness cannot fixate their eyes, tactile stimulation is a promising alternative. Tactile stimulation has been successfully used to facilitate brain-computer interface-based communication with healthy volunteers and patients with Locked-in Syndrome (Brouwer & van Erp, 2010; Kaufmann, Holz, & Kübler, 2013; Lugo *et al.*, 2014; Ortner, Prückl, & Guger, 2013; van der Waal, Severens, Geuze, & Desain, 2012). Some healthy volunteers also report that tactile feedback seems more natural than visual or auditory feedback in brain-computer interface paradigms (Chatterjee, Aggarwal, Ramos, Acharya, & Thakor, 2007; Cincotti *et al.*, 2007). Furthermore, brain-computer interfaces that use tactile stimulation may be more feasible in activities of daily living because these approaches leave the auditory and visual systems free for other applications (Maye, Zhang, Wang, Gao, & Engel, 2011; Zhang *et al.*, 2007).

Many previous assessments of the somatosensory system in patients with disorders of consciousness pertain to pain perception. A common paradigm involves the application of noxious electrical stimulation to the patient's wrist to determine whether the patient can sense or perceive pain (Boly *et al.*, 2008; Laureys, 2005). Notably, this technique has strong prognostic value in that patients who lack cortical responses to somatosensory stimuli whilst in an acutely comatose state are very unlikely to recover awareness (Zandbergen, de Haan, Stoutenbeek, Koelman, & Hijdra, 1998). In contrast, the approach described here involves the administration of non-painful vibrotactile stimulation to a patient's wrists and upper back. The prognostic value of this type of stimulation is currently unknown, and the large-scale clinical studies needed to evaluate prognosis are beyond the scope of this thesis. Importantly, it is also not appropriate to attribute awareness *per se* to brain responses in the absence of self-report. Nevertheless, the tactile stimulation used in this work can provide caregivers with more insight into the patient's probable subjective experience, including whether the patient responds to touch at the cortical level and exhibits differential cortical responses to changes in touch.

In this chapter, a hierarchical cognitive assessment of attention based on tactile stimulation is described. Each participant was presented with repetitive vibrotactile stimulation to the upper back alongside relatively more infrequent vibrotactile stimulation of the wrists. Stimulation was applied at a high, uniform rate to elicit a marker of sensory perception called the steady-state evoked potential (Picton, John, Dimitrijevic, & Purcell, 2003; Regan, 1977; Snyder, 1992). Infrequent stimulation was also applied to the wrists to elicit an event-related potential correlate of attention called the P300 (Comerchero & Polich, 1999; Picton, 1992; Polich, 2007). Although steady-state responses have not been extensively studied in this patient population (Chatelle *et al.*, 2012), some patients with disorders of consciousness can generate P300s (*e.g.*, Faugeras *et al.*, 2011, 2012; Fischer *et al.*, 2010; Hauger *et al.*, 2015; Schnakers *et al.*, 2008; Steppacher *et al.*, 2013). P300 responses also have similar morphological and topographic characteristics when generated by somatosensory, auditory, and visual stimuli (Kaufmann *et al.*, 2013; Lugo *et al.*, 2014; van der Waal *et al.*, 2012; Yamaguchi & Knight, 1991a, 1991b).

The vibrotactile attention task probed selective attention. Specifically, participants were instructed to selectively attend to the infrequent wrist stimuli by counting vibrations on a designated target wrist, *i.e.*, their left or right wrist. This manipulation was intended to elicit changes in the P300 due to top-down, conscious processing (Comerchero & Polich, 1999; Squires, Donchin, Herning, & McCarthy, 1977). If successful, the counting aspect of the task could eventually be applied in future communicative applications of the paradigm (*e.g.*, attend left wrist to answer "yes", *etc.*). The selective attention measure also dissociated between endogenous and exogenous attentional processing in the patients, and thus provided additional insight into their cognitive abilities (Chennu *et al.*, 2013; Chennu & Bekinschtein, 2012).

In total, a sample of fourteen patients with severe brain injuries and a group of healthy volunteers underwent a hierarchical cognitive assessment based on vibrotactile stimulation and EEG. Importantly, patients were also evaluated using two previously established fMRI-based assessments of covert command following; one fMRI-based assessment involved mental imagery (Owen *et al.*, 2006), and the other involved selective auditory attention (Naci & Owen, 2013). All patients underwent clinical behavioural assessments with the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005). By identifying patients with the ability to covertly and overtly follow commands, these additional assessments ensured a more accurate representation of each patient's residual cognitive abilities. Furthermore, these repeated assessments provided an opportunity to test the divergence and convergence of all techniques. It was expected that event-related potential markers of higher-order attention would be evident in patients with the ability to follow commands.

4.2 Materials and methods

4.2.1 Participants

Fourteen patients [mean age 41 (range: 19 to 58) years] contributed sufficient data for inclusion in this investigation. Seven patients were diagnosed as being in a Vegetative State (Royal College of Physicians Working Group, 2003); four patients were diagnosed as being in a Minimally Conscious State; two patients were diagnosed as emergent from a Minimally Conscious State (Giacino *et al.*, 2002); and one patient was diagnosed with Locked-in Syndrome (Smith & Delargy, 2005). Six patients had sustained traumatic brain injuries from motor vehicle accidents. The remaining eight patients had sustained non-traumatic brain injuries from different aetiologies including cardiac arrest (3 cases) and near drowning (1 case). Each patient's substitute decision maker provided informed, written consent for the patient's participation in the study. Ethical approval was obtained from the University of Western Ontario's Health Sciences Research Ethics Board (London, Ontario, Canada).

As a scientific control, a sample of fifteen healthy volunteers also participated in the somatosensory selective attention task. These participants ranged in age from 17 to 23 years (mean age of 18 years). All healthy volunteers provided informed written consent and received course credit for their participation. The Psychology Research Ethics Board of the University of Western Ontario (London, Ontario, Canada) provided ethical approval for the control study. Control studies of the other neuroimaging paradigms have been reported elsewhere (Boly *et al.*, 2007; Gabriel *et al.*, 2015; Naci, Cusack, Jia, & Owen, 2013).

4.2.2 Procedure

For each patient, this study comprised participation in three experimental paradigms:

(1) A somatosensory selective attention paradigm using EEG;
(2) An auditory selective attention paradigm using fMRI (Naci *et al.*, 2013; Naci & Owen, 2013); and
(3) A mental imagery paradigm using fMRI (Bardin *et al.*, 2011; Boly *et al.*, 2007; Fernández-Espejo & Owen, 2013; Gibson, Fernández-Espejo, *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006; Stender *et al.*, 2014).

Immediately prior to his or her participation in each experiment, each patient also underwent a behavioural assessment using the Coma Recovery Scale-Revised (Kalmar & Giacino, 2005). The fMRI data from Patient EMCS2 could not be analysed due to excessive motion artefacts. However, this patient was included in this investigation because his ability to follow simple commands and communicate was evident from his overt behaviour. Similarly, the data for Patient VS7 from one fMRI session (selective auditory attention, Experiment 2) were discarded due to excessive movement. This patient was included in the current investigation because useable data were obtained from this patient for the other two experimental paradigms. Details of the Coma Recovery Scale behavioural outcomes for all patients are available in Appendix D.

All patients completed the two fMRI paradigms within a two-day period. Ten patients completed the fMRI assessments within two days of their EEG assessments. The other four patients completed the EEG assessments after the fMRI assessment with the following delay: 1.5-months (EMCS1); 7.5-months (MCS3); 1-year (VS3); and 3.5-years (VS7). Only Patient MCS3 demonstrated a clinical status change between her assessments with EEG and fMRI (Minimally Conscious State *Minus* to Minimally Conscious State *Plus*). Given the aetiology, age, and time *post-ictus* of those patients with a year or more between assessments (Appendix D), it is unlikely (although not impossible) that either of these patients underwent a change in their conscious states between assessments (Multi-Society Task Force on PVS, 1994a, 1994b; Royal College of Physicians Working Group, 2003). Indeed, Patients VS3 and VS7 demonstrated overt behaviour consistent with a Vegetative State at all assessments.

4.2.2.1 Experiment 1: Somatosensory selective attention with EEG

Participants completed a short somatosensory selective attention task as their electroencephalograms were recorded. One stimulator was affixed to each wrist and the upper back for a total of three stimulators per participant. Each stimulator administered non-painful vibrotactile stimuli via a motor housed in a rubberized casing (Ortner *et al.*, 2013). A similar paradigm has also been evaluated for patients with Locked-in Syndrome (Lugo *et al.*, 2014). The experiment comprised 14 blocks. Participants were presented with a series of vibrations alternating among their wrists (10% per wrist) and upper back (80%). A vibration occurred every 200 ms and lasted for 50 ms. The number of vibrations presented to each wrist in a block was randomly selected from a uniform interval of 28 to 32. There was always a minimum of three (maximum=21) upper back stimuli between wrist vibrations; on average, 49% (standard deviation=13%) of the wrist stimuli followed exactly three upper back stimuli. Participants were instructed to count the vibrations only presented to the target wrist. The experimenter touched the patient's target wrist after the instruction. The right wrist was always the target wrist for the first block and subsequently alternated between the left and right wrists. The healthy volunteers reported their count at the end of each block; these participants reported the correct number of vibrations for 12 of 14 blocks on average, and all reports were within ±3 of the true number of targets. One block of trials lasted for approximately one minute.

4.2.2.2 Experiment 2: Auditory selective attention with fMRI

The fMRI selective auditory attention paradigm has been previously described in healthy individuals (Naci *et al.*, 2013) and patients with disorders of consciousness (Naci & Owen, 2013). In brief, this task was designed to identify the ability to follow a command pertaining to selective attention. On each trial, participants were instructed to either count a target word ("yes" or "no") presented among pseudorandom distractors (spoken digits one to nine), or to relax. Each trial had an on/off design of about 22.5 seconds of sound followed by 10 seconds of silence, and each scan lasted five minutes, including instructions.

4.2.2.3 Experiment 3: Command following with fMRI

During an fMRI scan, patients were asked to engage in two mental imagery paradigms (Bardin *et al.*, 2011; Boly *et al.*, 2007; Fernández-Espejo & Owen, 2013; Gibson, Fernández-Espejo, *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006; Stender *et al.*, 2014). In the motor imagery task, patients were instructed to imagine swinging their right arm to hit a tennis ball. In the spatial navigation task, patients were instructed to imagine moving from room to room in their house whilst visualising all the objects they would encounter. Instructions were delivered with noise cancellation headphones (Silent Scan^{TM}, Avotec Inc. for patients scanned in the Trio system, as well as Patient VS6 [first visit], and Sensimetrics S14 for the patients scanned in the Prisma system, including Patient VS6 [second visit]). Patients VS1, VS2, VS4, VS5, VS6 (second visit), MCS4, and EMCS1 completed two sessions of each task, while patients VS3, VS6 (first visit), VS7, MCS1, MCS2, MCS3, and LIS1 completed only one session due to scanner availability or suspected patient fatigue. Each task alternated five 30-second blocks of mental imagery and five 30-second blocks of rest for a total of five minutes per scan.

4.2.2.4 Replication data

Patients VS4, MCS3, and EMCS1 participated in second assessments with the somatosensory selective attention task and the Coma Recovery Scale. These assessments occurred from 2 to 3.5 months following their initial participation. Patient VS6 completed a second assessment comprising her participation in all three experimental paradigms and the Coma Recovery Scale 22-months after her initial participation. All four patients maintained the same clinical status at follow-up (Appendix D).

4.2.3 EEG data acquisition and pre-processing

EEG data were recorded at sites FC1, Fz, FC2, C3, Cz, C4, CP1, CP2, Pz, Oz, PO7, and PO8 using an electrode cap with the g.Gamma active electrode system (g.tec Medical Engineering GmbH, Austria). This montage was selected following a previous study conducted in patients with Locked-in Syndrome (Lugo *et al.*, 2014) and previous work concerning optimal P300 classification (Krusienski *et al.*, 2006). Data were sampled at 256 Hz and filtered between 0.5 and 30 Hz using a digital Butterworth filter. Stimuli were presented with the g.VIBROstim box (g.tec Medical Engineering GmbH, Austria) using a custom Matlab script for Simulink® (Mathworks, Inc., Natick, MA). The recordings were referenced to the right earlobe with a forehead (Fpz) ground with impedances below 5 kΩ at the beginning of the EEG recording.

Offline data processing was conducted with EEGLAB (Delorme & Makeig, 2004). The data were segmented into 1-second epochs including data from 200 ms prior to stimulus onset. Linear detrending and baseline correction were applied to each epoch. For artefact correction, all trials containing data with voltages exceeding ±100 µV were rejected. In a second step, the kurtosis of the signal across all channels was separately calculated for each stimulus type, and all trials exceeding 2.5 standard deviations of the mean were rejected. Final trial numbers are reported in Table 8.

Table 8. Trials remaining following artefact rejection for Experiment 1 in Chapter 4

	Stimulus Type *Mean* *(Minimum−Maximum)*			
	Upper Back	**Target Wrist**	**Non-Target Wrist**	**Trials Rejected (%)**
Patients (*n*=14)	2614 (1591−3246)	313 (188−384)	311 (180−388)	35 (20−59)
Controls (*n*=15)	2890 (2718−5026)	345 (327−363)	345 (321−359)	25 (20−32)

Notes. A 2x3 Chi-square goodness of fit test indicated that the minimum number of trials in each of the three stimulus types did not significantly differ between the controls and patients at the group level, $\chi^2(2)=0.21$, $p=0.9$.

4.2.4 fMRI data acquisition and pre-processing

The MRI data were acquired in a 3 Tesla Siemens scanner (Siemens, Erlangen, Germany) with a Siemens 32-channel head-coil at the Centre for Functional and Metabolic Mapping (Robarts Research Institute, Western University, Canada). The patients were recruited over 30-months, in which time the 3 Tesla scanner was upgraded. Three patients (VS3, VS7, and MCS3) were scanned in a Magnetom Trio system. All other patients were scanned in a Magnetom Prisma system. Functional echo-planar images of 36 slices covering the whole brain were acquired (repetition time=2,000 ms, echo time=30 ms, matrix size=420x420, slice thickness=3 mm, in-plane resolution=3×3 mm, flip angle=78°; for patients VS6 and LIS1 only, matrix size=384x384 and flip angle=75°). High-resolution T1-weighted three-dimensional images were acquired in the same session (Trio system: repetition time=2,300 ms, echo time=2.98 ms, inversion time=900 ms, matrix size=256×240, voxel size=1 mm^3, flip angle=9°; Prisma system: repetition time=2,300 ms, echo time=2.32 ms, inversion time=900 ms, matrix size=256x256, flip angle=8°; for patients VS6 and LIS1 only, matrix size=240x256 and flip angle=9°). Data from the mental imagery paradigm were pre-processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm), as described in Chapter 3 (Gibson, Fernández-Espejo, *et al.*, 2014). For the selective attention paradigm, the same pre-processing was performed with the Automatic Analysis software (Cusack *et al.*, 2014).

4.2.5 Statistical analyses

4.2.5.1 Experiment 1: Somatosensory selective attention with EEG

The EEG data were assessed for the presence of a steady-state evoked potential to the repetitive vibrotactile stimulation. As one vibration occurred every 200 ms, an evoked response was considered present when the averaged peak of the frequency spectrum of the data at the stimulation rate (5 Hz) and its first harmonic (10 Hz) was significantly higher than the background noise (Dobie & Wilson, 1996). A frequency spectrum was calculated with a discrete Fourier transform over the entire 1-second epoch from the average of all trials only using data from site Pz (Mouraux *et al.*, 2011; Tobimatsu, Zhang, & Kato, 1999). An F ratio (alpha=.05; $F_{2,20}$>=3.49) was computed to compare the power at 5 and 10 Hz with the average power in the ten adjacent frequency bins (2−4 Hz, 6−9 Hz, and 11−13 Hz; Dobie & Wilson, 1996).

Two analyses of the EEG data were conducted to identify the attention-based event-related potentials. For the bottom-up attention effect, responses to wrist (deviant) and upper back (standard) stimuli were compared. A pseudorandom subset of the standard stimuli (equal in number to the deviant stimuli) was selected because there were many more standard than deviant stimuli. For the top-down attention effect, responses to the target and non-target wrist stimuli were compared. Trial numbers were matched between the target and non-target trials.

Of note, the event-related potential comparisons in this work employ cognitive definitions of top-down and bottom-up attention. However, the resultant contrasts differ from the classic event-related potential contrasts for bottom-up and top-down attention, known as the P3a and P3b event-related potentials, respectively (Polich, 2007). Specifically, the classic P3a effect involves a contrast of responses to non-target deviant and standard stimuli, and the classic P3b effect involves a contrast of target deviant and standard stimuli. In this work, the bottom-up event-related potential effect involves a contrast of responses to all deviant stimuli (target and non-target) and all standard stimuli.

This contrast has more statistical power than the conventional P3a contrast because more deviant trials are available. This approach also corresponds with a cognitive definition of attentional orienting. One potential shortcoming of this approach, however, is that the resultant event-related potential could contain correlates of top-down attention from the target deviant stimuli (Bonfiglio & Carboncini, 2016). Importantly, a cognitive subtraction approach is also used to isolate top-down attention in this paradigm, *i.e.*, target deviant versus non-target deviant stimuli. This approach is necessary because a deviant stimulus is only a target if the participant selectively attends to that deviant stimulus when instructed (Gibson *et al.*, 2016a). If the participant does not comply with task instructions, the conventional P3b contrast for top-down attention (target versus standard) could return a significant effect driven by attentional orienting to deviant stimulation. This concern is particularly relevant for the patients in this study who could not overtly confirm that they understood and followed task instructions. Accordingly, the event-related potential effects in this work are not referred to as P3a and P3b event-related potentials and are instead described as bottom-up (or P3a-like) and top-down (or P3b-like) event-related potential effects.

In the event-related potential analyses, data from 50 to 750 ms relative to stimulus onset were analysed using the cluster-mass procedure of the Matlab toolbox FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011). This technique was described in detail in Chapters 2 and 3 (Gibson, Fernández-Espejo, *et al.*, 2014; Gibson, Chennu, Owen, & Cruse, 2014), and elsewhere (Cruse *et al.*, 2014; Maris & Oostenveld, 2007). Briefly, data were first compared at each time-point using a t test. In the second step, the t values of adjacent spatiotemporal points with $p<.05$ were summed to form clusters. The largest cluster was retained. This entire procedure was repeated 1,000 times with recombination and randomized resampling of the event-related potential data. This Monte Carlo method generated a nonparametric estimate of the p value representing the statistical significance of the originally identified cluster.

4.2.5.2 Experiment 2: Auditory selective attention with fMRI

The general linear model (SPM8) was used to explore effects of interest. Two event types were defined corresponding to the on/off periods (count/relax, or vice-versa). The silent period served as an implicit baseline for all trials. Events for these regressors were modelled by convolving boxcar functions with the canonical hemodynamic response function. The following nuisance variables were also included in the general linear model: the movement parameters in the three directions of motion and three degrees of rotation, and the mean of each scan. Linear contrasts were used to obtain subject-specific estimates for the effect of interest. Clusters with $p<.05$ after the familywise error correction were reported as significant.

4.2.5.3 Experiment 3: Command following with fMRI

Single-subject fixed-effect analyses were performed for each patient. The analysis was based on the general linear model using the canonical hemodynamic response function (Friston, Holmes, Poline, Price, & Frith, 1996) implemented with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The analysis pipeline was previously reported in Chapter 3 (Gibson, Fernández-Espejo, *et al.*, 2014). Linear contrasts were used to obtain subject-specific estimates, and results were thresholded at a voxel level, whole-brain family-wise error-corrected $p<.05$. When no significant activations were found at this level, the statistical threshold was reduced to an uncorrected $p<.001$ because of the strong anatomical *a priori* hypotheses (Bardin *et al.*, 2011; Boly *et al.*, 2007; Fernández-Espejo & Owen, 2013; Gibson, Fernández-Espejo, *et al.*, 2014; Monti *et al.*, 2010; Owen *et al.*, 2006; Stender *et al.*, 2014). This less conservative threshold excluded the possibility of failing to detect more subtle changes in the signal (Fernández-Espejo *et al.*, 2010; Friston *et al.*, 1996).

4.3 Results

All patient outcomes are summarized in Table 9. Additional details concerning each patient's outcomes on the Coma Recovery Scale are available in Appendix D.

Table 9. Summary of patient demographics and experimental outcomes in Chapter 4.

ID (Diagnosis)	Sex/Age (years)/ Interval *post-ictus* (years)	Aetiology	Evoked Potential (EEG)	P300 (EEG)	Voluntary Behaviour (CRS-R)	Mental Imagery (fMRI)	Selective Auditory Attention (fMRI)
VS1 (VS)	M/19/4.0	Non-traumatic	Present	Absent	Absent	Absent	Absent
VS2 (VS)	F/51/0.9	Non-traumatic	Present	Absent	Absent	Absent	Absent
VS3 (VS)	M/57/3.1 (fMRI) 58/4.1 (EEG)	Non-traumatic	Present	Absent	Absent	Absent	Absent
VS4 (VS)	F/42/4.3	Non-traumatic	Present	Absent	Absent	Absent	Absent
VS5 (VS)	F/52/6.5	Non-traumatic	Present	Absent	Absent	Absent	Absent
VS6 (VS/MCS*)	F/44/20.4 (Test 1) 46/22.2 (Test 2)	Traumatic	Present	Present (Test 1) Absent (Test 2)	Absent	Present	Present
VS7 (VS/MCS*)	M/23/6.0 (fMRI) 26/9.5 (EEG)	Traumatic	Present	Present	Absent	Present	N/A (motion)
MCS1 (MCS-)	M/40/3.1	Traumatic	Present	Absent	Absent	Absent	Present
MCS2 (MCS+)	M/35/16.9	Non-traumatic	Present	Present	Object localisation Reproducible movement to command	Absent	Present
MCS3 (MCS+)	F/47/19.8	Non-traumatic	Present	Present	Reproducible movement to command	Present	Present
MCS4 (MCS-)	F/25/5.7	Traumatic	Present	Present	Absent	Present	Present

ID (Diagnosis)	Sex/Age (years)/ Interval *post-ictus* (years)	Aetiology	Evoked Potential (EEG)	P300 (EEG)	Voluntary Behaviour (CRS-R)	Mental Imagery (fMRI)	Selective Auditory Attention (fMRI)
EMCS1 (EMCS)	F/49/12.3	Traumatic	Present	Present	Functional object use Functional and accurate communication	Present	Absent
EMCS2 (EMCS)	M/32/4.1	Traumatic	Present	Present	Functional object use Functional and accurate communication	N/A (motion)	N/A (motion)
LIS1 (LIS)	M/55/1.5	Brainstem infarct	Present	Present	Functional and accurate communication	Present	Present

Notes. CRS-R=Coma Recovery Scale-Revised; fMRI=functional magnetic resonance imaging; EEG=electroencephalography; VS=Vegetative State; MCS=Minimally Conscious State; EMCS=emergent from a Minimally Conscious State; LIS=Locked-in Syndrome; M=male; F=female; N/A=not applicable.

4.3.1 Experiment 1: Somatosensory selective attention with EEG

A steady-state evoked potential was detected in the EEG data of all healthy volunteers (*n*=15; Figure 8) and all patients (*n*=14; Figure 9).

Bottom-up attention effects (deviant versus standard stimuli) were detected from eight patients and all the healthy volunteers (*n*=15; Figure 10). All patients who demonstrated a differential response to the deviant versus standard stimuli also demonstrated command following in either a behavioural or a neuroimaging-based assessment (Figure 13).

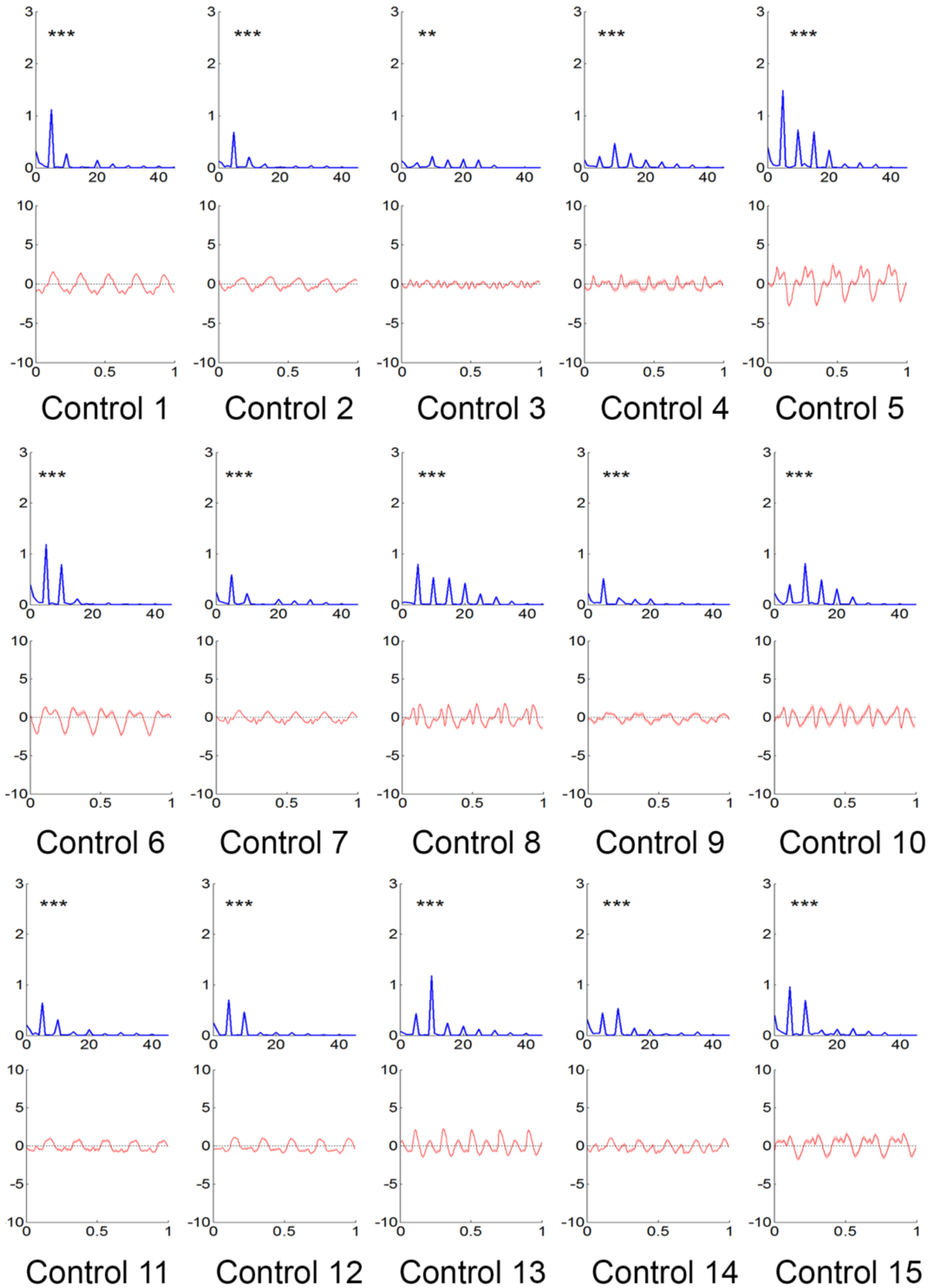

Figure 8. Steady-state evoked responses from the healthy volunteers in Chapter 4.

Power spectra (top panels) and averaged EEG responses (bottom panels) calculated over a 1-second period. Analyses were conducted using the data recorded from site Pz only; each waveform (bottom panels) is depicted with ±1 standard error of the mean in colour-matched shading. **=p<0.01; ***=p<.001.

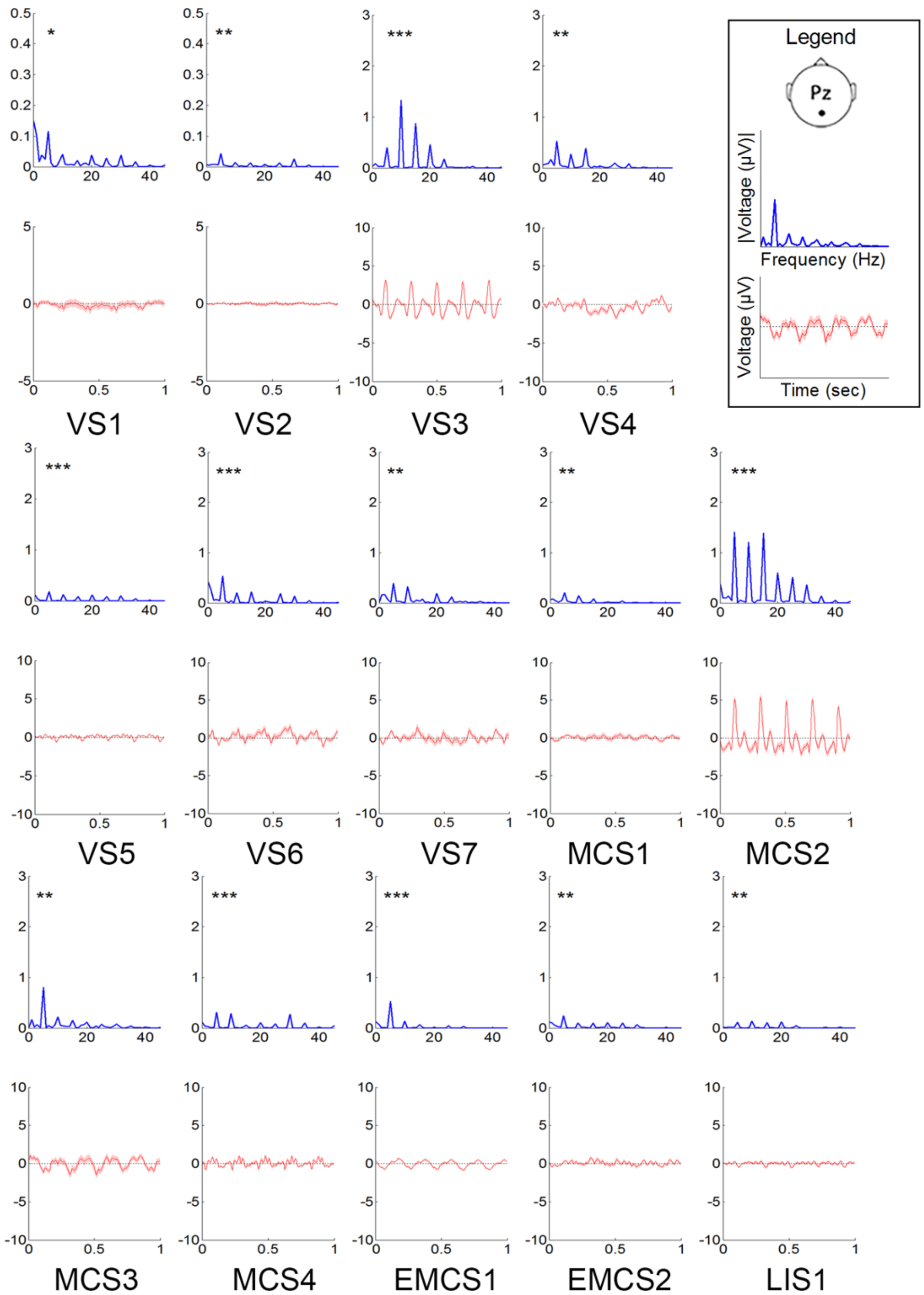

Figure 9. Steady-state evoked responses from the patients in Chapter 4.

Power spectra (top panels) and averaged EEG responses (bottom panels) calculated over a 1-second period. Analyses were conducted using the data recorded from site Pz only; each waveform (bottom panels) is depicted with ±1 standard error of the mean in colour-matched shading. *=p<0.05; **=p<0.01; ***=p<.001.

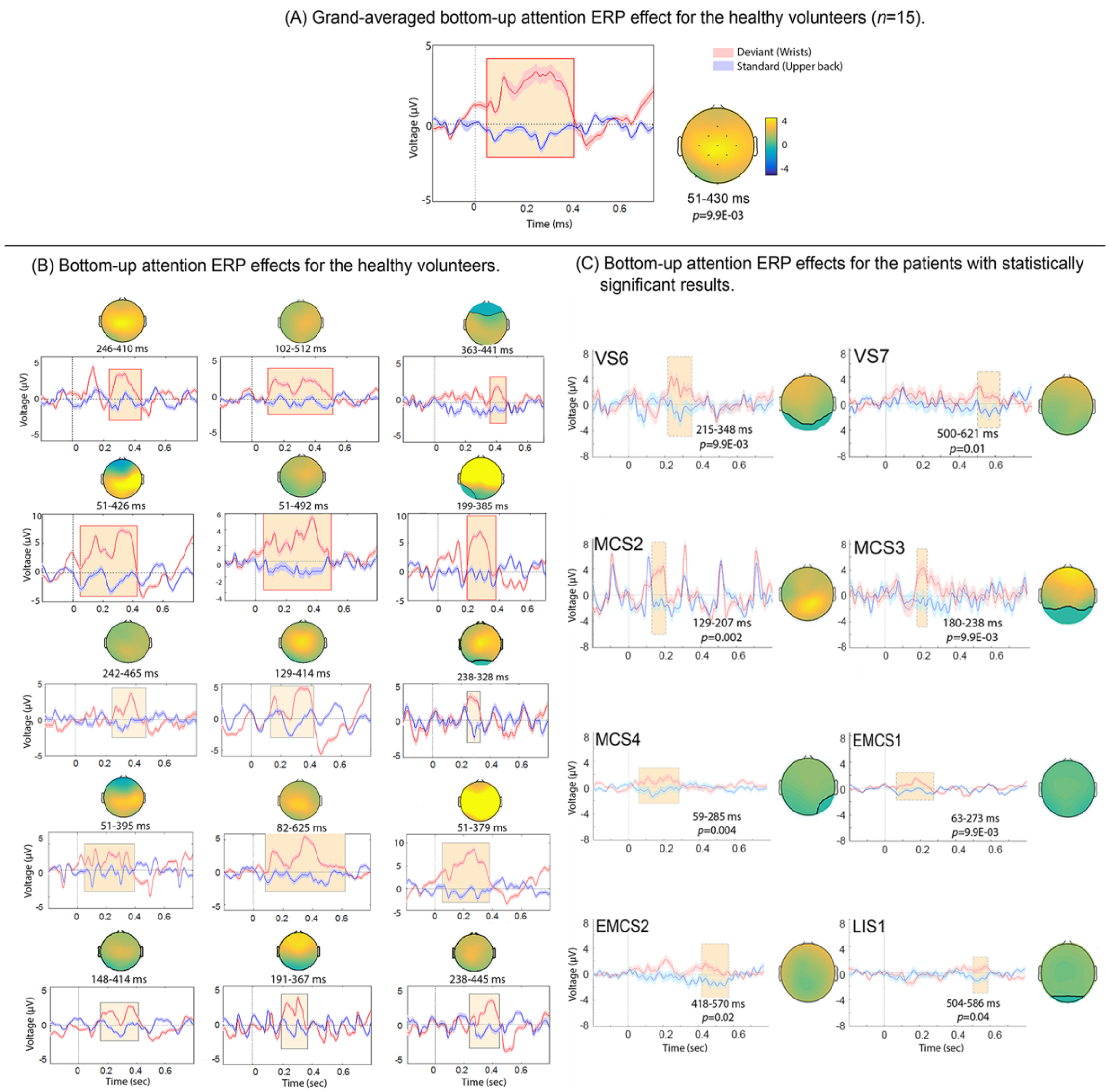

Figure 10. Bottom-up attention event-related potentials from Chapter 4.

Spatiotemporal clusters were calculated across all twelve electrodes and are depicted with ±1 standard error of the mean in colour-matched shading. The electrodes included in the significant spatiotemporal cluster are enclosed with a black line on each topographic plot. Panel A depicts the grand-averaged and Panel B depicts the single-subject event-related potential effects for the healthy volunteers (p<9.9E-03 in all cases). Panel C depicts the single-subject event-related potential effects for patients with statistically reliable results.

Top-down event-related potential attention effects (target versus non-target wrist vibrations) were not detected from any of the patients. However, this event-related potential effect was evident for healthy volunteers at the group level (*n*=15) and at the single-subject level, albeit with a hit-rate of 67% (Figure 11). Hit-rates of at least 80% (12/15) and 100% (15/15) have been reported for fMRI-detected mental imagery and selective attention, respectively (Naci *et al.*, 2013). Given the low sensitivity of the top-down attention event-related potential analysis (*i.e.*, 67%), additional *post-hoc* comparisons were conducted. While the number of trials available after artefact rejection did not differ across groups (Table 8; $\chi^2(2)=0.21$, $p=0.9$), some patients had many fewer useable trials available than healthy volunteers. The single-subject event-related potential analyses for the healthy volunteers were thus repeated in the *post-hoc* analyses using only a pseudorandom subset of trials equal in number to the minimum number of trials available in the single-subject analyses of the patient data (180 trials, in the case of Patient MCS2).

Bottom-up attentional event-related potential effects were detected at the single-subject level for all healthy volunteers when as few as 180 trials were included for each stimulus type. However, top-down attentional event-related potential effects were detected from only seven healthy volunteers. Subsequent analyses revealed that a minimum of 300 trials were required to detect the top-down attentional event-related potential effects from the same 10 healthy volunteers as in the *a priori* analyses. Four patients did not have enough data available to meet this criterion. Overall, these analyses indicate that the top-down attentional event-related potential effect may not have been detected in some single-subject analyses due to low trial numbers. Nevertheless, the bottom-up attentional event-related potential effect was robust to data loss.

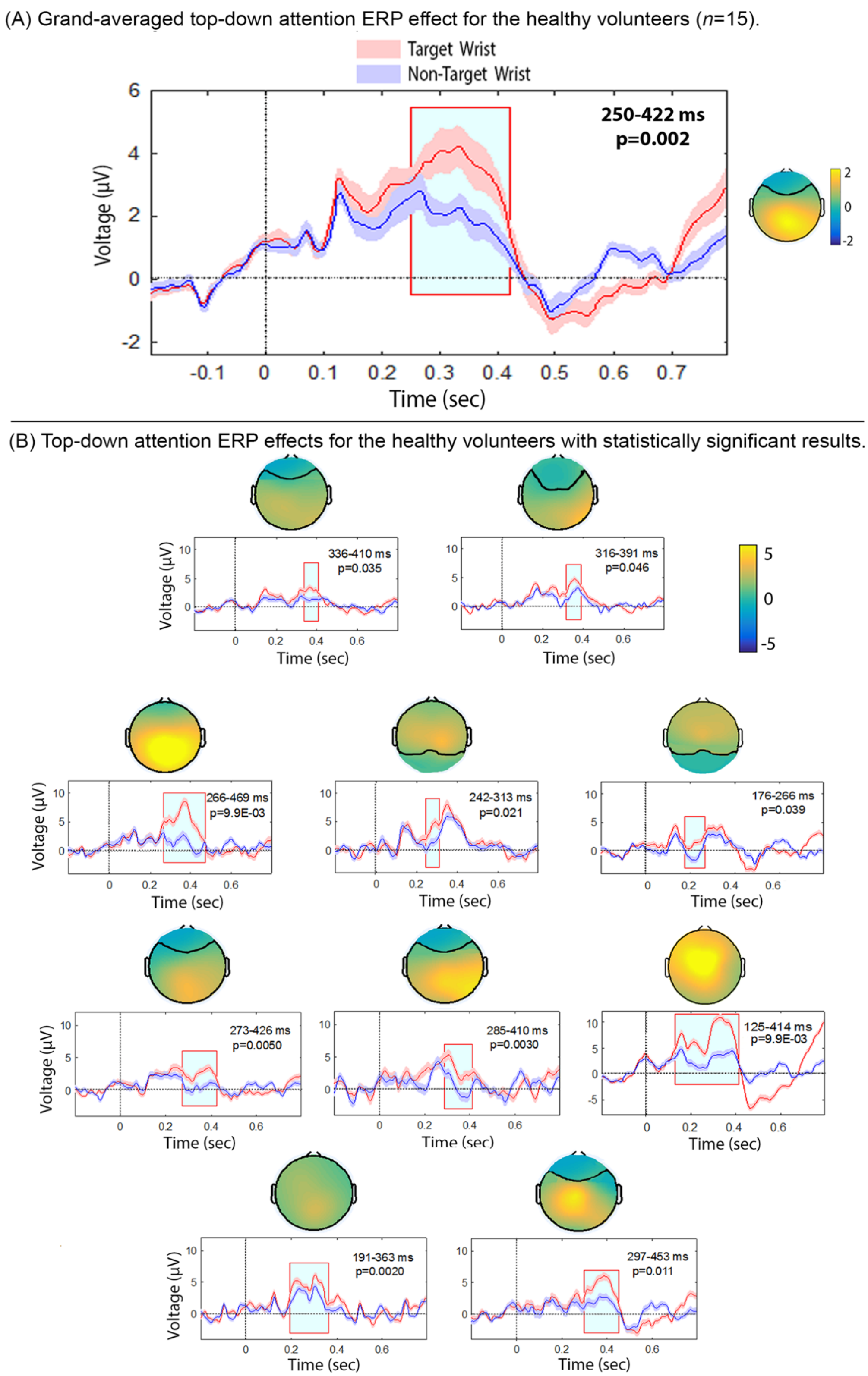

Figure 11. Top-down attention event-related potentials from Chapter 4.

Spatiotemporal clusters were calculated across all twelve electrodes with each waveform depicted with ±1 standard error of the mean in colour-matched shading. The electrodes included in the significant spatiotemporal cluster are enclosed with a black outline on each topographic plot. The grand-averaged result (*n*=15) is depicted in (A). For the single subject results (B), only results from participants with statistically significant clusters are shown.

4.3.2 Experiment 2: Auditory selective attention with fMRI

The results of each patient from all fMRI assessments (Experiments 2 and 3) are summarized in Figure 12. Of the patients diagnosed as being in a Vegetative State, only Patient VS6 generated a statistically differential hemodynamic response following the instruction to count as compared to the instruction to relax. Specifically, this patient exhibited increased activation in the temporal and parietal cortex bilaterally (family-wise error-corrected at $p<.05$). Patients MCS1-4 and LIS1 also produced more hemodynamic activation following the instruction to count than the instruction to relax (family-wise error-corrected at $p<.05$ in each case). The regions differentially activated by these patients are as follows: Patient MCS1, frontotemporal and parietal cortex bilaterally; Patient MCS2, temporal cortex bilaterally; Patient MCS3, parietal cortex bilaterally; Patient MCS4, frontotemporal and parietal cortex bilaterally; and Patient LIS1, frontotemporal cortex bilaterally. Notably, Patient EMCS1 did not show differences in activation in the command following task even though she was able to follow commands with her overt behaviour immediately prior to her assessment. Patients VS7 and EMCS2 were excluded from this analysis because both patients moved excessively during their functional scan.

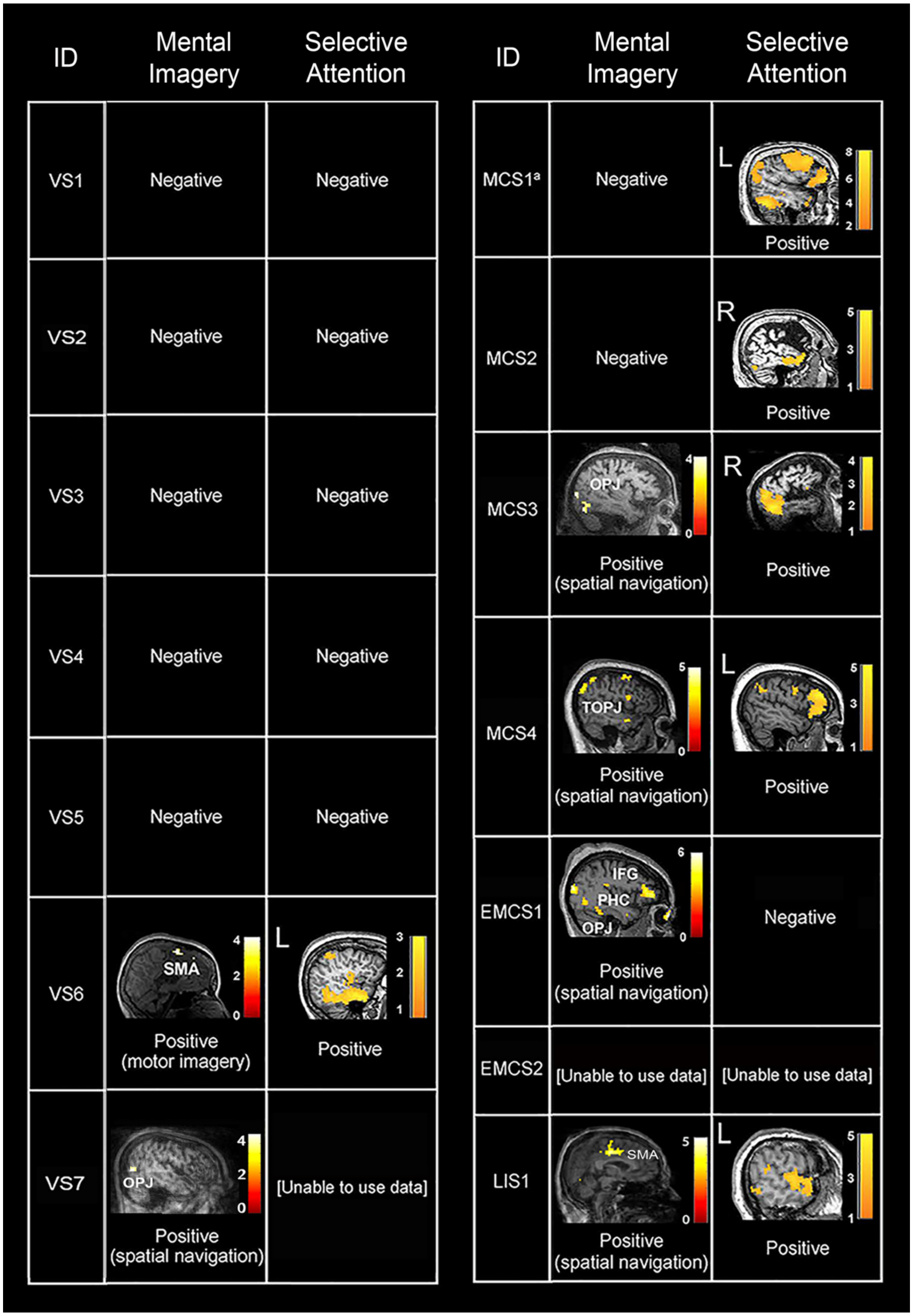

Figure 12. Summary of fMRI outcomes from Chapter 4.

SMA=supplementary motor area; OPJ=occipito-parietal junction; TOPJ=temporo-occipito-parietal junction; PHC=parahippocampal cortex; IFG=inferior frontal gyrus.

Only positive results are depicted. For the fMRI mental imagery paradigms, significant task-related fMRI activation is labelled by region (Imagery>Rest), and results are thresholded at an uncorrected $p<.001$. For the fMRI selective auditory attention task, only activation clusters within the attention network (Count>Relax) that survived the familywise error correction threshold of $p<.05$ at the whole-brain level are displayed. All fMRI results are rendered on each patient's T1 anatomical MRI image, and scales depicting the statistical maps (*t* values) are inset.

[a]Patient MCS1 scored in the Vegetative State range immediately prior to his participation in the EEG assessment. However, this patient scored in the Minimally Conscious State *Minus* range in another CRS assessment several hours prior to his participation in this EEG investigation. For this reason, this patient has been classified as being in a Minimally Conscious State *Minus*.

4.3.3 Experiment 3: Command following with fMRI

The results of each patient from all fMRI assessments (Experiments 2 and 3) are summarized in Figure 12. In her first visit, Patient VS6 produced reliable, appropriate activation during the motor imagery task in the supplementary motor area and cerebellum bilaterally at an uncorrected $p<.001$ (cluster level family-wise error-corrected $p<.05$). In her second visit, Patient VS6 produced reliable, isolated clusters of activation during the motor imagery and spatial navigation tasks in the left precentral gyrus at an uncorrected $p<.001$ (cluster level family-wise error-corrected $p<.05$). The patient was thus reclassified as being in a non-behavioural Minimally Conscious State (Gosseries, Zasler, & Laureys, 2014). Patients VS7 showed high levels of motion requiring 37% and 37.5% of his data to be discarded for motor imagery and spatial navigation, respectively. The analysis of the remaining data only revealed appropriate activation during the spatial navigation task (*i.e.*, the left occipito-parietal junction at uncorrected $p<.001$.). The patient was also reclassified as being in a non-behavioural Minimally Conscious State (Gosseries *et al.*, 2014).

Patients MCS3, MCS4, EMCS1, and LIS1 also only showed reliable activation during the spatial navigation task. This involved: bilateral occipito-parietal junction (uncorrected

$p < .001$) for MCS3; right temporo-occipito-parietal junction (family-wise error-corrected $p < .05$), as well as right dorsal premotor cortex, right insular cortex, and right putamen (uncorrected $p < .001$) for MCS4; right occipito-parietal junction, a region in the boundaries between right lingual gyrus/parahippocampal cortex, left precentral gyrus (comprising the supplementary and pre-supplementary motor areas), as well as some less typical areas such as the inferior frontal gyrus, the left superior temporal gyrus, and the left striatum (family-wise error-corrected $p < .05$) for EMCS1; and the supplementary motor area, right precentral gyrus, occipito-parietal junction, posterior temporo-occipital region, and cerebellum (uncorrected $p < .001$) for LIS1. The remaining seven patients (VS1-5, MCS1, and MCS2) showed no activation at the conservative family-wise error-corrected statistical threshold, or at uncorrected $p < .001$.

4.3.4 Correspondence between command following and EEG responses

The main hypothesis in this investigation was that patients who were aware would exhibit EEG markers of higher-order attention processing. While top-down processing was not detected in the event-related potentials from any patients, an interesting relationship is evident between a specific marker of awareness—command following—and the bottom-up event-related potential effect. A patient was considered aware if he or she demonstrated command following in any one of the three assessments not based upon EEG responses (*i.e.*, selective auditory attention, mental imagery, or a behavioural assessment with the Coma Recovery Scale). This approach is consistent with clinical behavioural guidelines in which a diagnosis of awareness (Minimally Conscious State) is given if a patient reliably follows a command across multiple trials (Kalmar & Giacino, 2005). A Fisher's exact test revealed a significant positive association between command following and event-related potential evidence of bottom-up attention ($p = .007$; note $p = .0047$ if the two observations of Patient VS6 are not included to maintain the assumption of independence). This relationship is summarised in Figure 13.

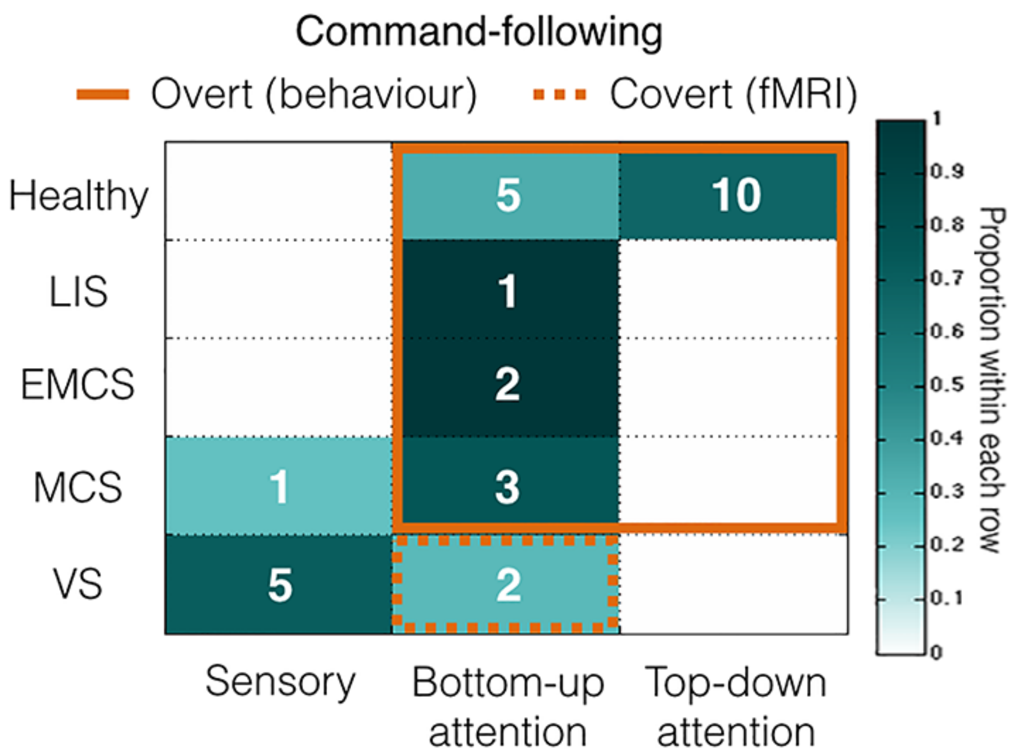

Figure 13. Summary of the relationship between command following and the EEG outcomes of Experiment 1 in Chapter 4.

fMRI=functional magnetic resonance imaging; VS=Vegetative State; MCS=Minimally Conscious State; EMCS=emergent from a Minimally Conscious State; LIS=Locked-in Syndrome. The summary depicts the number of patients and healthy volunteers who generated each of the three possible outcomes (*i.e.*, sensory response [steady-state evoked potential], bottom-up attention [event-related potential], or top-down attention [event-related potential]) on the somatosensory selective attention task (Experiment 1, EEG).

4.3.5 Replication data

The replication results are depicted in Figure 14. All patients exhibited consistent effects across assessments apart from Patient VS6. For Patient VS6, the bottom-up attention event-related potential effect was only detected during her initial assessment.

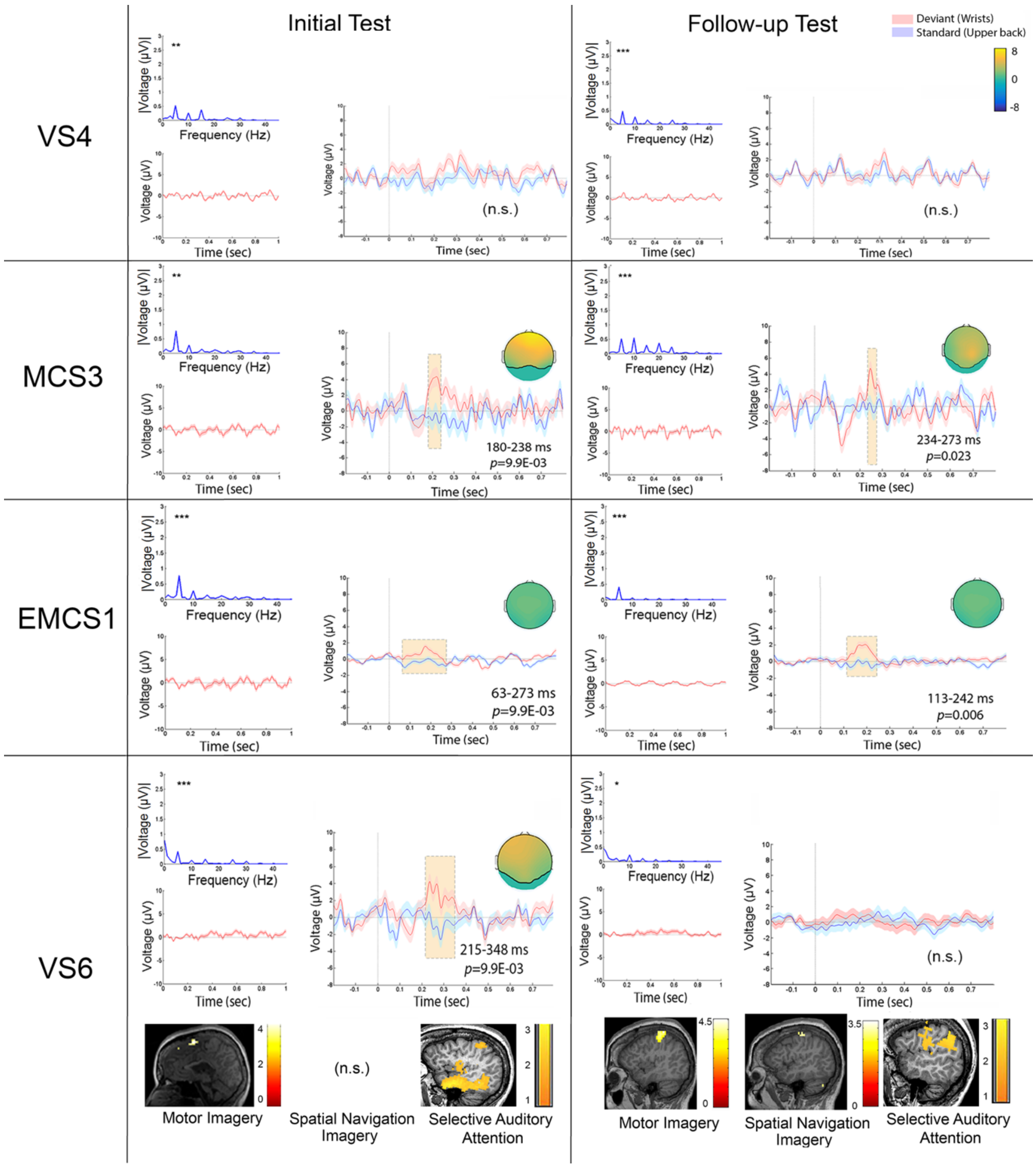

Figure 14. Replication data from the follow-up visits with some patients in Chapter 4.

Data are depicted for the initial and follow up tests of Patients VS4, MCS3, EMCS1, and VS6, as labelled. For the steady-state evoked potentials, power spectra (top left panels within each cell) and averaged EEG data (bottom left panels within each cell) were calculated over a 1-second period. Analyses were conducted using the data recorded from site Pz only; each waveform is depicted with ±1 standard error of the mean in colour-matched shading. For the bottom-up attention event-related potential effects (right panels within each cell), spatiotemporal clusters were calculated across all twelve electrodes and are depicted with ±1 standard error of the mean in colour-matched shading. The electrodes included in the significant spatiotemporal cluster are enclosed with a black line on each topographic plot. The temporal boundaries and the probability value of each cluster are indicated with shading and inset text. For Patient VS6 only, two separate fMRI assessments were conducted at each testing session. For the fMRI mental imagery paradigm, significant task-related fMRI activation is depicted (Imagery>Rest), and results are thresholded at an uncorrected $p<.001$. For the fMRI selective auditory attention task, only activation clusters within the attention network (Count>Relax) that survived the familywise error correction threshold of $p<.05$ at the whole-brain level are displayed. The fMRI results are rendered on the patient's T1 anatomical MRI image, and scales depicting the statistical maps (*t* values) are inset.

*=$p<0.05$; **=$p<0.01$; ***=$p<.001$; n.s.=not statistically significant.

4.4 Discussion and conclusions

In this chapter, fourteen patients with severe brain injuries underwent a novel EEG-based assessment of residual sensory and cognitive processing. The EEG outcomes were compared with two fMRI-based assessments of covert command following and one behavioural assessment of overt command following. The primary novel finding of this work was the relationship between an event-related potential marker of bottom-up attention orienting and command following. Specifically, all patients with the event-related potential bottom-up attention effect (P300) demonstrated command following. Similarly, most patients who did not generate an event-related potential marker of bottom-up attention also did not demonstrate command following (Figure 13).

Some investigators have reported positive prognostic value in the presence of a P300 following traumatic brain injury (Cavinato *et al.*, 2009; Lew *et al.*, 2003). There have also been reports of correlations between cognitive event-related potentials and behavioural markers of awareness (Kotchoubey *et al.*, 2005; Schnakers *et al.*, 2008). Furthermore, other investigators have found that cognitive event-related potentials are predictive of recovery in patients with acute disorders of consciousness (Steppacher *et al.*, 2013; Wijnen, van Boxtel, Eilander, & de Gelder, 2007). Crucially, the current study included two neuroimaging-based assessments of covert command following. This step is important given that a recent meta-analysis estimated a 15% rate of covert awareness among patients diagnosed as being in a Vegetative State (Kondziella *et al.*, 2016). Previous studies of the P300 in patients with disorders of consciousness are likely to have included patients capable of covert command following, thus obscuring the relationship reported here. While the feasibility of routine neuroimaging assessments in clinical practice is limited by health, safety, and financial factors, the findings of this work suggest that these assessments are necessary to elucidate the relationship between a patient's conscious state and his or her residual sensory and cognitive abilities.

It is curious that an event-related potential marker of unconscious (or preconscious) processing is closely linked to awareness in this work. Indeed, the classic event-related potential marker of bottom-up attention, the P300, can be elicited by unattended stimuli and during REM sleep and deep sedation (Chennu & Bekinschtein, 2012; Polich, 2007). It may be that the correspondence between the event-related potential marker of bottom-up attention and command following stems from the overlap of the neural networks that support attention. Such networks are relatively more preserved in conscious patients (Fernández-Espejo *et al.*, 2012; Thibaut *et al.*, 2012). Moreover, frontal lobe lesions have been associated with diminished P300 responses to auditory and somatosensory stimulation (Knight, 1984; Yamaguchi & Knight, 1991a). Notably, this association suggests that a P300 response may be less informative for patients with specific frontal lobe injuries. Nevertheless, a P300 can be elicited without the explicit collaboration of the individual—*i.e.*, without following task instructions (Chennu & Bekinschtein, 2012). This feature is appealing because it suggests that a passive assessment of attention orienting, which entails lower cognitive demands than active assessments of voluntary top-down attention, may be sufficient to identify patients with covert awareness.

The P3b-like event-related potential marker of top-down attention was not detected from any of the patients in this sample. A similar finding has been previously reported in one study of patients in a Minimally Conscious State (Pokorny *et al.*, 2013). It has also been suggested that the single-subject sensitivity of the P3b is too low for clinical awareness detection (Höller *et al.*, 2013). While the single-subject sensitivity of the P300 is typically 100% in healthy volunteers, the single-subject sensitivity of the P3b ranges from about 44% to 70% (Höller *et al.*, 2011, 2013; Kotchoubey, Lang, Herb, Maurer, & Birbaumer, 2004). Notably, P3b-like event-related potentials in the current work were detected from only 67% (10/15) of the healthy volunteers when relying upon a cognitive subtraction to isolate top-down attentional processing. However, the conventional P3b contrast yielded a hit-rate of 100% from the healthy volunteers. As highlighted in the Methods section, this conventional contrast does not necessarily isolate top-down attention in this paradigm. Indeed, the conventional P3b contrast of target deviant versus standard is no different from the conventional P300 contrast of non-target deviant versus standard if the participant does not comply with the instruction to selectively attend to certain deviant stimuli. For this reason, a cognitive subtraction (target deviant versus non-target deviant) is needed quantify any differences in responses to deviant stimuli due to top-down, selective attention. Alternatively, the oddball task used in this investigation frequently involved the presentation of a deviant stimulus after three standard stimuli (49% of trials). Greater variability in the rate of deviant stimulus presentation may reduce expectancy effects and elicit more stable P3b-like event-related potentials in future work. Finally, the P3b effect was not detected from any patients in this study using either the cognitive subtraction technique or the conventional contrast. For this reason, it is not clear from this investigation whether event-related potential markers of top-down attention will facilitate the differential diagnosis of disorders of consciousness.

As a final consideration, time-variant levels of arousal and fatigue characteristic of disorders of consciousness may have led to inconsistent engagement in the EEG counting task (Giacino, Fins, Laureys, & Schiff, 2014; Whyte *et al.*, 2013). Participants were required to sustain attention for five minutes in blocks of about twenty-two seconds for both fMRI tasks, whereas the EEG task involved fifteen minutes of attention in blocks of about one minute. The EEG task was longer to ensure that a high EEG signal-to-noise ratio was achieved, and *post-hoc* analyses confirmed that the top-down event-related potential effect was sensitive to data loss. Unfortunately, increased task duration requires participants to sustain attention for an even longer period and may have contributed to the low sensitivity of this marker in the patient cohort. Some investigators use machine learning to circumvent these issues and address possible time-dependent variations in the electrocortical responses of patients with brain injuries (*e.g.*, King *et al.*, 2013). For simplicity of interpretation and consistency with clinical methods, however, a more traditional event-related potential voltage comparison was used in the current work. Notably, statistical reliability was assessed with permutation testing following the recommendations of other researchers in this field (Billinger *et al.*, 2013; Goldfine *et al.*, 2013; Noirhomme *et al.*, 2014). Although machine-learning techniques may have rendered a more sensitive description of time-variant results, the analyses were conducted in line with recommended practice for this type of translational research.

In closing, the determination of whether patients with disorders of consciousness are aware is a clinical standard of care. To influence clinical practice, it is essential to compare novel assessments with existing techniques. The current investigation directly compared two previously established fMRI-based assessments of covert command following (Naci & Owen, 2013; Owen *et al.*, 2006) and one novel EEG-based hierarchical cognitive assessment (Gibson *et al.*, 2016b). The results of the fMRI assessments converged for nine of the twelve patients with useable data from both paradigms, and an EEG marker of attentional orienting (the P300) identified patients with the ability to follow commands. The behavioural profile of disorders of consciousness—that is, time-variant fatigue and arousal—always affords the possibility that a patient did not demonstrate covert command following due to lack of voluntary engagement in the mental task. Likewise, false negatives occur in assessments of healthy volunteers (*e.g.,* Cruse *et al.*, 2011; Fernández-Espejo, Norton, & Owen, 2014). Nevertheless, the less than perfect correspondence of the assessments of covert command following reported here may have occurred because the demands of a given task were better suited to some patients than others. For example, some individuals find it difficult to engage in motor imagery (Hammer *et al.*, 2011; Vidaurre & Blankertz, 2010), and in some reports, brain-computer interfaces driven by the neural correlates of selective attention are successfully operated by more users than brain-computer interfaces driven by the neural correlates of imagined movement (Guger *et al.*, 2009; Guger, Edlinger, Harkam, Niedermayer, & Pfurtscheller, 2003). Accordingly, assessments of covert command following based on selective attention may be better suited to a general population. Overall, however, an optimal evaluation of a patient with a disorder of consciousness should include multiple assessments to maximise the likelihood of detecting responses that are not evident from overt behaviour. In the absence of unambiguous ground truth, an investigation of the concordance between assessments may be the best way to improve diagnostic and prognostic accuracy.

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Chapter 5

5 General Discussion

5.1 Key contributions and limitations

Patients with disorders of consciousness have significant behavioural impairments due to their severe brain injuries. Patients in a Vegetative State exhibit no voluntary behaviour and lack awareness of all external stimulation, while patients in a Minimally Conscious State exhibit variable, but reproducible, voluntary behaviour and awareness (Bernat, 2006). It is difficult to differentially diagnose disorders of consciousness, and neural correlates of minimal versus absent awareness are occasionally used to complement and supplement behavioural evaluations (Giacino, Fins, Laureys, & Schiff, 2014; Laureys, 2005; Owen, 2013). A small number of patients diagnosed as being in a Vegetative State demonstrate covert awareness through appropriate and reliable modulations of their brain activity in response to verbal commands (Bardin, Schiff, & Voss, 2012; Cruse *et al.*, 2011; Goldfine, Victor, Conte, Bardin, & Schiff, 2011; Owen *et al.*, 2006). The aim of this thesis was to improve existing EEG-based assessments of covert command following and cognition to further facilitate the differential diagnosis of disorders of consciousness at the bedside. Novel techniques were validated in healthy volunteers, and all patients underwent assessments based upon behaviour, EEG, and fMRI. Strategies to improve the sensitivity of single-subject analyses of neuroimaging data were discussed in all empirical chapters, including customised mental tasks and distinct neural correlates of the mental processes of interest.

Together, the three experiments described in this thesis have advanced the scientific and clinical understanding of disorders of consciousness in at least two ways. Firstly, paradigms and stimuli that are customized to a participant can result in more reliable single-subject outcomes. Indeed, the primary finding of Chapter 2 was that musicians generated enhanced responses to motor imagery involving musical performance relative to motor imagery of other actions. The customisation of the motor imagery task to the participants' previous experiences accordingly resulted in a more sensitive detection of volitional brain responses. Unfortunately, customised motor imagery did not facilitate the detection of covert command following from the small sample of patients with disorders of consciousness in Chapter 3. Nevertheless, this study involving patients contributed to the second major finding of this thesis: assessments of multiple cognitive abilities, supported by distinct brain regions and neural signatures, are needed to characterise a patient's level of residual cognition. Indeed, many patients in Chapters 3 and 4 demonstrated covert command following in only one assessment. For instance, one patient in Chapter 3 had selective damage to cortical motor areas; this patient did not produce a reliable brain response to motor imagery, but she did produce a robust brain response to mental imagery involving spatial navigation. In Chapter 4, an event-related potential marker of attentional orienting (the P300) identified patients with the ability to follow commands. This finding indicates that a simple bedside assessment of oddball detection may be sufficient to identify patients with residual cognitive abilities or awareness. Notably, multiple assessments of the same patient in Chapters 3 and 4 did not always yield converging results; for example, some patients did not exhibit both EEG- and fMRI-based responses to motor imagery (Chapter 3) or selective attention (Chapter 4). Nevertheless, if the patients discussed in this thesis had been assessed on just one occasion, or repeatedly with the same mental task, their covert cognitive abilities may have never been identified. Accordingly, customized assessments that probe a patient's abilities in more than one sensory domain and with more than one neural correlate are a promising way to minimise false negatives in the detection of covert cognition and awareness.

A common limitation of all three empirical chapters in this thesis is the possibility of attribution errors. Attribution errors in the detection of covert cognition and awareness carry significant consequences. Among other possibilities, patients may receive unsuitable care, medical resources may be inappropriately used, and families may suffer unnecessary emotional distress or financial loss (Jox, Bernat, Laureys, & Racine, 2012; Peterson, Cruse, Naci, Weijer, & Owen, 2015). In terms of false negatives—*i.e.*, the failure to attribute awareness to a patient who is aware, validation studies with healthy volunteers can eliminate some confounding factors in patient assessments. For example, healthy volunteers can overtly confirm or deny their conformance with tasks demands to identify the neural correlates of compliant, successful task performance. However, assessments of patients with severe brain injuries are designed to be response-free with low cognitive demands; findings based on the responses of healthy volunteers to simple cognitive tasks may not generalise to patients. Additionally, 10 to 30% of healthy volunteers generate negative results in mental imagery paradigms under optimal performance conditions (Vidaurre & Blankertz, 2010). Single-subject effects may also differ from group effects in neuroimaging paradigms due to variations in individual brain structure. Moreover, patients may produce negative results because they do not understand a task, or because they temporarily exhibit reduced responsiveness secondary to a medical comorbidity. In future work, healthy volunteers could be instructed to ignore commands in some blocks of trials to characterise the neural correlates of interest during volitional inhibition (Owen *et al.*, 2007). Similarly, target neural responses could be validated during natural fluctuations in vigilance, such as distraction or drowsiness (Chennu & Bekinschtein, 2012). Nevertheless, it may be impossible to identify the ground truth about awareness in the absence of self-report, and false negatives in the attribution of awareness are a pervasive challenge in studies of patients with disorders of consciousness.

False positives—*i.e.*, the ascription of awareness to a patient who is not aware—are also possible in the attribution of covert awareness. False positives may occur due to variations in statistical thresholds and analysis techniques. Statistical corrections for multiple comparisons and restrictions of analyses to brain or scalp regions of interest are commonly used in neuroimaging studies to reduce false positives (Bennett, Wolford, & Miller, 2009; Kilner, 2013; Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Similarly, permutation tests are preferred to binomial tests to reduce false positives in the statistical assessment of classification outcomes in this field (Cruse, Chennu, *et al.*, 2013; Goldfine *et al.*, 2013; Noirhomme *et al.*, 2014). Additionally, however, false positives may occur if a brain response of interest does not correlate with a volitional mental process. For example, linguistic stimuli in mental imagery paradigms could elicit involuntary neural responses (Greenberg, 2007; Nachev & Husain, 2007). Indeed, action words such as “kick” or “lick” correlate with a few seconds of activation in brain areas associated with motor function (Hauk, Johnsrude, & Pulvermüller, 2004). Notably, unconscious mental representations persist for a few seconds or less (Greenwald & Draine, 1996; Naccache *et al.*, 2005). The prolonged responses (30 seconds) necessary in fMRI-based assessments of covert command following accordingly provide compelling evidence of sustained, and arguably conscious, responses to verbal commands (Dehaene & Naccache, 2001; Naccache, 2006; Owen *et al.*, 2007). As an additional consideration, the incidence of positive neuroimaging results is lower than the incidence of negative neuroimaging results in studies of covert awareness. For example, approximately 15% of patients diagnosed as being in a Vegetative State can covertly follow commands (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016), and only about 45% of patients who could overtly follow commands also demonstrated covert command following in one large clinical validation study (Stender *et al.*, 2014). Nevertheless, clinicians and scientists must ensure that appropriate analytical techniques and construct validity are applied to the clinical determination of awareness, regardless of whether positive or negative results are obtained.

5.2 Understanding consciousness via acquired brain injury

Historically, acquired and congenital brain injuries have provided unique opportunities to study cognition and perception in humans (Thiebaut de Schotten *et al.*, 2015). For example, the famous patient Henry Molaison (“H.M.”) had a large portion of his medial temporal lobe removed to treat intractable epilepsy (Scoville & Milner, 1957). Although this surgery resulted in profound memory loss for the patient, his subsequent participation in research significantly advanced understanding of the hippocampus and other medial temporal lobe structures in human memory (Eichenbaum, 2013). Moreover, this patient and the subsequent understanding of his abilities and impairments helped guide surgical practice toward the minimally invasive protocols used today (Mauguiere & Corkin, 2015). It may be that patients with disorders of consciousness, who present with profound disruptions to the behaviours commonly ascribed to awareness, provide a similar opportunity to study consciousness in humans.

The bad news about the scientific study of consciousness, particularly when relying upon patients with disorders of consciousness, is both logistical and philosophical in nature. Firstly, it is difficult to obtain a sufficient quantity of high-quality neural data from patients with disorders of consciousness. Most patients lack voluntary motor control and exhibit fluctuations in arousal. Accordingly, patients who remain alert throughout an assessment are likely to move, and patients who do not move during an assessment may not be alert or awake. The former scenario results in data loss due to motion-related artefacts, while the latter scenario results in data with insufficient construct validity to assess conscious processing. Furthermore, patients with disorders of consciousness typically have severe and diffuse acquired brain injuries. Findings concerning the neural structures or functions that support conscious processing in these patients may not generalize to persons with healthy brains. As a second consideration, it is difficult to operationalize conscious processing. There are several philosophical, psychological, and neurobiological perspectives on the neural correlates of consciousness (*e.g.*, Chalmers, 2000; Dennett & Kinsbourne, 1992; Hohwy, 2009; Rees, Kreiman, & Koch, 2002). However, consensus has not yet been reached as to how best measure consciousness within existing theoretical frameworks (Block, 2007; Seth, Dienes, Cleeremans, Overgaard, & Pessoa, 2008). For instance, self-report is one of the only widely accepted techniques to identify self-awareness (Naccache, 2006; Weiskrantz, 1997). Unfortunately, it is unclear whether the neural mechanisms that underlie self-report, especially those pertaining to linguistic and gestural communication, can be isolated from the neural mechanisms that underlie awareness (Block, 2007; Lamme, 2006; Seth *et al.*, 2008). This issue is particularly problematic for patients with disorders of consciousness; most patients with disorders of consciousness cannot overtly respond, and yet patients who can follow commands using neural correlates of volitional mental tasks exhibit compelling evidence of awareness (Owen, 2013; Stins & Laureys, 2009).

Notwithstanding its inherent limitations, the scientific study of consciousness involving patients with disorders of consciousness has elucidated the now classic distinction between wakefulness and awareness in human subjective experience. It is remarkable that a person can survive a catastrophic brain injury; present with an apparent absence of all voluntary behaviour and responsiveness to external stimulation; and yet retain cycles of wakefulness and quiescence. In a healthy brain, the brainstem ascending reticular activating system regulates cyclical wakefulness through diffuse afferent connections to the thalamus and cerebral cortex (Moruzzi & Magoun, 1949; Plum & Posner, 1972). Many patients with disorders of consciousness present with periods of wakefulness and non-wakefulness because their reticular activating systems are spared from injury, whilst insults to other brain structures lead to the profound disruptions in awareness characteristic of these disorders (Bernat, 2006). Owing in part to this dissociation between wakefulness and awareness in patients with disorders of consciousness, consciousness is now often described as a continuum of abilities with different modes of operation (Bayne & Hohwy, 2007; Blume, Del Giudice, Wislowska, Lechinger, & Schabus, 2015). Furthermore, awareness can persist in the absence of wakefulness. For example, healthy sleepers have demonstrated priming effects, movement preparation, and preliminary attentional processing in different stages of sleep (Bareham, Manly, Pustovaya, Scott, & Bekinschtein, 2014; Chennu & Bekinschtein, 2012; Hobson, 2009). Likewise, some patients with disorders of consciousness exhibit severely disrupted sleep architecture, and many patients possess no discernible circadian rhythm, even though they occasionally exhibit voluntary behaviour (Cologan *et al.*, 2010; Cruse, Thibaut, *et al.*, 2013; De Weer *et al.*, 2011). In light of these findings, a promising future direction in the scientific study of consciousness is to determine whether awareness can persist in the complete absence of wakefulness characteristic of the comatose state. Such evidence would provide a fascinating new perspective on our understanding of subjective experience via acquired brain injury.

From a scientific standpoint, preserved awareness in some patients with disorders of consciousness suggests that the neural correlates of consciousness are dependent on whole brain integrity rather than a designated brain structure *per se*. For example, some researchers posit that awareness is supported by two distinct cortical networks: (1) a network pertaining to external awareness of information perceived using the senses, and (2) a network pertaining to internal awareness of stimulus-independent thoughts (Demertzi *et al.*, 2011; Demertzi, Soddu, & Laureys, 2013; Heine *et al.*, 2012;

Vanhaudenhuyse *et al.*, 2011). Within these networks, activity in the frontoparietal network is impaired in most patients in a Vegetative State and in many healthy volunteers during slow wave sleep, deep anaesthesia, and absence seizures (Blumenfeld, 2012; Boveroux *et al.*, 2008; Cavinato *et al.*, 2015; Thibaut *et al.*, 2012). Additionally, it has been hypothesised that executive function, which correlates with activity in frontoparietal brain networks, could serve as a cognitive proxy for human consciousness (Naci, Cusack, Anello, & Owen, 2014; Naci & Owen, 2013). From a functional perspective, executive function enables an organism to process information from the external environment to make predictions and plan behaviours (Stuss & Knight, 2013). In this respect, executive function is the cognitive equivalent of generating an internal experience from external stimulation and may accordingly index conscious processing. Finally, many state-of-the-art psychological hypotheses posit that consciousness arises from wide-scale brain function (*e.g.*, Cleeremans, 2011; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Tononi, 2004). Patients with disorders of consciousness provide valuable opportunities to evaluate and refine all models of conscious processing, and the study of these patients continues to inform leading theoretical accounts of consciousness as a psychological construct.

The most impactful discovery in the scientific study of consciousness via acquired brain injury may pertain to the patients with disorders of consciousness themselves. There is robust evidence that patients in a Vegetative State lack both behavioural and neural responses to external stimulation (Bernat, 2006). Some patients in a chronic Vegetative State exhibit cerebral metabolism arguably more similar to brain death than healthy wakefulness (Laureys, Owen, & Schiff, 2004). It is very unlikely that patients with chronic disorders of consciousness, particularly those in a Vegetative State, will regain functional independence (Royal College of Physicians Working Group, 1996, 2003). Nevertheless, clinicians and most other people are appropriately cautious to designate any patient as completely ‘unaware’, and early neuroimaging-based research supported this intuition by demonstrating that some patients in a Vegetative State could engage in complex information processing (*e.g.*, Owen *et al.*, 2002; Schiff *et al.*, 2002). After about a decade of additional study, it is now acknowledged that a substantial minority of patients in a Vegetative State can volitionally modulate their brain activity in response to command (Giacino *et al.*, 2014; Gosseries, Zasler, & Laureys, 2014; Kondziella *et al.*, 2016; Owen *et al.*, 2006). It is a fascinating and somewhat incidental scientific finding that the neural mechanisms thought to support awareness can persist following such profound disruption. For the small number of patients with residual awareness, however, the detection of covert command following may be life changing, particularly if their ability to communicate is restored.

5.3 Recommendations and future directions

Recent advancements in neuroimaging technology and technical computing have led to innovative developments in neuroscience research and related medical practice. Our understanding of the abilities of patients with disorders of consciousness has been substantially advanced by assessments that are not contingent on motor output and instead rely on brain responses. Significantly, it is now understood that some patients who lack overt responsiveness following catastrophic brain injury can exhibit sleep-wake cycles and engage in voluntary regulation of their brain activity in response to command. Although these two findings are revolutionary for the clinical understanding of patients with disorders of consciousness, and provide some insight into the neural basis of consciousness in general, the study of disorders of consciousness needs new growth. Three promising ways forward are discussed next with reference to the findings of this thesis and the relevant current literature.

The first area of recommended growth for the study of disorders of consciousness is the conduct of large-scale, multicentre, clinical validation studies. Indeed, this manner of inquiry may be the only way forward for medical purposes (Laureys & Schiff, 2012). Some physicians and other people involved in patient care are sceptical of neuroimaging-based approaches, even though these approaches facilitate differential diagnosis in some cases (Owen, 2013). This scepticism arises in part because many people adopt behaviourist approaches to assess awareness (Kurthen, Moskopp, Linke, & Reuter, 1991; Plum & Posner, 1972). Furthermore, most investigations that use neuroimaging rely upon single cases or small, heterogeneous cohorts of patients with disorders of consciousness to validate techniques. These small-scale investigations provide valuable proof-of-concept for future clinical trials, but do not provide sufficient evidence to warrant adoption in standard medical practice. Additionally, the primary aim of most neuroimaging-based investigations involving patients with disorders of consciousness is to facilitate differential diagnosis. However, the prediction of recovery, especially during the acute treatment phase, is at least equally as important from a clinical perspective. A few candidate neural markers of recovery exist: for example, patients with higher cerebral metabolism, or resting EEG with higher complexity, are more likely to recover awareness (Babiloni *et al.*, 2009; Bagnato *et al.*, 2010; Di, Boly, Weng, Ledoux, & Laureys, 2008; Stender *et al.*, 2016). Unfortunately, the prediction of the absence of recovery is more reliable than the prediction of recovery (Stender *et al.*, 2014; Wijdicks, Hijdra, Young, Bassetti, & Wiebe, 2006). Accordingly, investigations concerning the neural markers of positive prognosis in the acute treatment phase are needed. With appropriate validation in large, multicentre cohorts of patients, neuroimaging-based techniques will significantly advance knowledge and standards of care pertaining to diagnosis, prognosis, and medical management of patients with disorders of consciousness.

A second avenue of progress for the study of disorders of consciousness is the implementation of feedback in brain-computer interface-based paradigms intended to support two-way communication with these patients. It is unlikely that many patients will possess the cognitive resources needed to communicate with a brain-computer interface; to the best of my knowledge, fewer than ten patients with disorders of consciousness have communicated using neuroimaging techniques to date (Bardin *et al.*, 2012; Fernández-Espejo & Owen, 2013; Forgacs *et al.*, 2014; Monti *et al.*, 2010; Naci & Owen, 2013). Nevertheless, other patients with prolonged immobility from severe motor impairments have already benefited from brain-computer interfaces. For example, state-of-the-art brain-computer interfaces have provided patients who are quadriplegic with a reasonably sophisticated ability to grasp objects using a mechanical arm (Hochberg *et al.*, 2006, 2012). Other brain-computer interfaces have provided patients who are paralysed with the ability to create simple graphic designs (Münßinger *et al.*, 2010). Similarly, a few patients diagnosed as being in a Minimally Conscious State have successfully operated brain-computer interfaces presented as simple video games, such as moving a ball to a basket with motor imagery or selecting a target photograph with a reward in a forced choice paradigm (Coyle, Carroll, Stow, McCreadie, & Mcelligott, 2013; Coyle, Stow, McCreadie, McElligott, & Carroll, 2015; Pan *et al.*, 2014). Notably, these successful brain-computer interfaces provide direct, online feedback to the user. Indeed, effective feedback provides users with positive reinforcement and entertainment to reduce frustration and fatigue (Kleih & Kübler, 2013; Nijboer, Birbaumer, & Kübler, 2010; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). Changes in feedback could also identify sleep onset or lack of interest (*e.g.*, a sudden drop in performance mid-session). While it is not known how many patients possess the cognitive resources needed to communicate using a brain-computer interface, the implementation of feedback is an important next step toward the restoration of communication and environmental control for patients with disorders of consciousness.

A third and final way forward for the study of disorders of consciousness pertains to ethical models of patient care. For example, a primary claim of this thesis is that multi-modal assessments are needed to minimize false negatives in the attribution of awareness. A patient is likely to exhibit divergent outcomes on different assessments due to the heterogeneous nature of severe, acquired brain injuries and the unusual behavioural profile characteristic of disorders of consciousness. Unfortunately, it is not yet clear how to interpret conflicting outcomes or to communicate feedback from contradictory findings to a care team or family member (Fins, 2013; Graham *et al.*, 2015). A primary concern is that positive evidence from only one assessment in a battery will undermine confidence in the positive result, even though the incidence of positive outcomes is lower than the incidence of negative outcomes overall. Alternatively, communication via fMRI has been a possibility since at least 2009 (Sorger *et al.*, 2009). Other neuroimaging techniques, such as functional near-infrared spectroscopy and EEG, also offer pragmatic solutions to issues of infrastructure and expense in standard clinical practice (Chatelle, Lesenfants, Guller, Laureys, & Noirhomme, 2015; Naci *et al.*, 2012; Naseer & Hong, 2015). The development of bedside brain-computer interface-based communication will accordingly warrant additional consideration of medical decision making for non-communicative patients. Although brain-computer interface output may be sufficient for the identification of at least minimal consciousness, there may be no level of confidence in communicative brain-computer interface output that is appropriately high to inform major medical decisions (Fins & Schiff, 2010; Mackenzie, 2013; Peterson *et al.*, 2013). As medical knowledge and related technology advances, it is essential to revisit the ethical framework pertaining to patient care to ensure that a patient's rights and best interests are respected (Fins, 2009; Weijer *et al.*, 2014).

5.4 Conclusions and extrapolations

The scientific and clinical understanding of patients with disorders of consciousness has been revolutionised by neuroimaging in the last twenty years. Nevertheless, the differential diagnosis of awareness remains a challenging clinical determination. In this thesis, neuroimaging-based assessments that probe a patient's abilities in more than one sensory domain and with more than one neural correlate were applied to reduce false negatives in the attribution of awareness. The novel EEG assessments were developed with reference to existing gold standards and implemented with relatively simple and inexpensive bedside acquisition protocols. Over the next twenty years, it is expected that some patients with disorders of consciousness will be able to communicate at the bedside using similar techniques. Such technology will be accessible and widely available owing to further advancements in commercial human-machine interfaces for healthy users. At that time, many patients will have experienced brain-facilitated device control prior to their injuries. These factors will in turn enhance a suitable patient's ability to demonstrate volitional modulations of his or her brain activity during rehabilitation. Notably, it is anticipated that patients with chronic disorders of consciousness will continue to reap no direct benefit from translational research because curative treatment will remain unlikely. Nonetheless, many patients will experience an improved quality of life because affordable brain-computer interfaces will provide them with entertainment, two-way communication, and correspondingly sensitive care. In short, research pertaining to disorders of consciousness in the next twenty years will continue to instigate positive changes and impactful scientific discoveries for researchers, clinicians, and patients alike.

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Appendices

Appendix A: Ethics approval.

Western Research — Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology,Western University

HSREB File Number: [redacted]
Study Title: Communication with brain measures
Sponsor:

HSREB Amendment Approval Date: September 02, 2014
HSREB Expiry Date: May 31, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Study End Date	end date extension to May 31, 2015	

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Amendment Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB[redacted]

Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Adrian Owen
File Number:[redacted]
Review Level: Delegated
Approved Local Adult Participants:[redacted]
Approved Local Minor Participants:[redacted]
Protocol Title:EEG assessment of sensory and cognitive functioning in patients with disorders of consciousness (REB #[redacted]
Department & Institution: Social Science\Psychology,Western University
Sponsor: Canadian Excellence Research Chair

Ethics Approval Date: August 29, 2013 **Expiry Date:**April 30, 2016
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Letter of Information	version July 2013	
Revised Western University Protocol	minor administrative change	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is [redacted] The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB [redacted]

[redacted]

Signature

Ethics Officer to Contact for Further Information

[redacted]	[redacted]	[redacted]

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Appendix C: Supplementary data for Chapter 2.

Supplementary Table C-1. Single-trial classification outcomes for Experiment 1 of Chapter 2.

	Simple Imagery vs. Rest			**Complex Imagery vs. Rest**		
Participant	**Acc**	**Time**	**#TP**	**Acc**	**Time**	**#TP**
1	59.13	3.9	0	56.97	3.1	0
2	66.70*	3.1*	24*	64.81*	3.1*	10*
3	60.87	2.3	0	60.43	3.3	0
4	57.36	3.9	0	68.76*	2.8*	25*
5	58.78	2.4	0	62.58*	3.8*	5*
6	61.80*	3.5*	3*	56.89	3.2	0
7	59.36	2.9	0	58.11	2.5	0
8	59.26	4.9	0	66.58*	3.4*	19*
9	59.71	2.5	0	60.35	3.0	0
10	66.43*	4.6*	26*	66.19*	4.3*	31*
11	64.42*	3.5*	6*	67.44*	4.6*	20*
12	57.81	2.4	0	64.23*	4.5*	12*
13	57.80	2.1	0	64.04*	3.7*	25*
14	61.57	3.1	0	63.10*	5.1*	4*
15	58.15	3.0	0	59.16*	4.5*	1*
16	61.74	3.6	0	64.14*	2.2*	4*
M	60.68	3.22	3.69	62.64	3.55	9.69
SE	0.74	0.20	2.13	0.93	0.21	2.71

Notes. Acc=maximum cross-validated classification accuracy (%); Time=time of Acc (seconds following offset of auditory cue); #TP=number of time points for which statistically reliable classification results were obtained; *M*=mean; *SE*=standard error of the mean.

*p<.05, with False Discovery Rate correction for multiple comparisons

Supplementary Table C-2. Single-trial classification outcomes for Experiment 2 of Chapter 2.

	Piano Imagery vs. Rest			Hockey Imagery vs. Rest			Hand Squeeze Imagery vs. Rest		
Participant	Acc	Time	#TP	Acc	Time	#TP	Acc	Time	#TP
Pianist									
1	63.45	3.2	14*	60.91	4.5	0	62.22	4.0	5
2	59.31	4.1	0	63.75	4.2	7	58.03	4.0	0
3	58.20	1.8	0	63.32	1.8	5	63.21	2.0	11*
4	60.15	2.0	0	62.36	2.7	0	56.96	3.6	0
5	68.24*	4.4*	39*	70.28*	4.4*	52*	61.78	4.1	0
6	56.67	3.3	0	59.72	4.9	0	57.66	1.3	0
7	66.02*	2.9*	32*	69.08*	2.9*	14*	62.53	2.0	5
8	76.25*	4.4*	71*	75.31*	5.2*	61*	57.09	5.1	0
9	69.76*	4.9*	29*	65.07	2.3	11*	67.92*	4.9*	21*
10	59.48	3.9	0	62.71	1.8	4*	62.74	2.9	5*
11	59.08	3.6	0	53.33	1.1	0	57.31	5.3	0
12	63.27*	5.2*	12*	58.21	3.9	0	56.05	3.9	0
13	57.50	3.7	0	54.97	1.1	0	65.09	4.5	7*
14	73.99*	4.3*	64*	63.85	4.2	4*	68.04*	4.2*	45*
15	59.78	3.9	0	59.75	3.0	0	53.97	1.8	0
16	61.81	4.9	0	61.24	4.8	0	61.49	2.0	0
M	63.31	3.76	16.31	62.74	3.27	9.88	60.76	3.45	6.19
SE	1.49	0.24	5.99	1.38	0.35	4.69	1.05	0.33	2.96
Hockey Player									
1	58.93	3.2	0	66.35*	2.3*	9*	62.33	4.2	0
2	56.74	5.5	0	55.24	3.4	0	52.71	1.5	0
3	59.45	1.7	0	66.64*	2.0*	10*	60.51	1.4	0
4	66.11*	3.3*	19*	59.58	2.2	0	69.05*	3.1*	42*
5	56.15	3.8	0	56.88	4.8	0	58.51	3.8	0
6	64.49	3.8	11*	69.15*	4.2*	32*	64.57*	3.7*	19*
7	56.88	1.1	0	60.20	3.6	0	59.78	4.0	0
8	56.38	2.6	0	56.90	3.1	0	56.99	2.5	0
9	57.26	4.9	0	59.26	4.9	0	56.56	5.3	0
10	55.95	3.6	0	57.89	3.1	0	54.02	2.6	0
11	59.59	3.3	0	52.26	3.4	0	63.43*	4.2*	9*
12	55.19	2.5	0	53.07	4.0	0	56.76	4.7	0
13	63.58*	1.5*	7*	59.52	1.8	0	58.76	4.5	0
14	67.03*	4.5*	25*	77.59*	4.2*	37*	61.57	2.7	5*
15	58.90	4.3	0	57.92	3.3	0	59.43	2.7	0
16	55.08	2.8	0	56.96	3.2	0	57.38	3.1	0
M	59.23	3.25	3.88	60.34	3.31	5.50	59.52	3.35	4.69
SE	0.98	0.31	1.95	1.64	0.24	2.95	1.02	0.28	2.80

Participant	Piano Imagery vs. Rest			Hockey Imagery vs. Rest			Hand Squeeze Imagery vs. Rest		
	Acc	Time	#TP	Acc	Time	#TP	Acc	Time	#TP
Control									
1	55.93	1.7	0	60.40	4.1	0	56.47	2.1	0
2	64.05	3.5	3*	69.09*	5.1*	19*	65.34	5.5	3*
3	62.08	2.9	0	68.41*	2.7*	18*	68.33*	2.7*	21*
4	58.30	3.4	0	61.32	4.3	0	59.63	2.8	0
5	54.89	4.3	0	57.70	4.2	0	58.43	2.9	0
6	62.36	5.3	0	72.71*	3.4*	52*	69.83*	5.5*	30*
7	58.08	4.9	0	59.03	2.5	0	60.55	2.5	0
8	60.28	2.7	0	60.51	2.7	0	66.79*	4.7*	10*
9	66.55*	2.6*	34*	62.31	3.8	6*	65.03*	3.5*	20*
10	62.13	2.5	4*	62.86	3.0	4*	65.34*	4.6*	25*
11	70.64*	1.4*	15*	63.94	1.4	4*	61.99	1.3	0
12	70.32*	3.3*	66*	64.07*	1.8*	13*	57.86	2.2	0
13	77.58*	4.1*	67*	77.16*	3.3*	64*	76.53*	3.3*	67*
14	59.02	4.4	0	57.31	1.9	0	58.18	1.7	0
15	61.86	3.1	4*	59.47	4.4	0	68.56*	4.5*	17*
16	65.89*	3.9*	14*	63.69	2.6	7*	60.22	2.8	0
M	63.12	3.35	12.94	63.75	3.18	11.69	63.69	3.25	12.06
SE	1.49	0.27	5.70	1.38	0.26	4.82	1.37	0.33	4.53

Notes. Acc=maximum cross-validated classification accuracy (%); Time=time of Acc (seconds following offset of auditory cue); #TP=number of time points for which statistically reliable classification results were obtained; *M*=mean; *SE*=standard error of the mean.

*p<.05, with False Discovery Rate correction for multiple comparisons

Supplementary Table C-3. Single-trial classification outcomes for Experiment 3 of Chapter 2.

Participant	Simple Piano Imagery vs. Rest			Complex Piano Imagery vs. Rest		
	Acc	**Time**	**#TP**	**Acc**	**Time**	**#TP**
1	74.10*	3.2*	45*	72.48*	2. 9*	64*
2	65.47*	3.5*	9*	64.29	3.7	9*
3	59.25	3.6	0	67.50*	2.7*	24*
4	61.32	4.3	0	60.47	3.3	0
5	60.46	3.9	0	71.67*	5.5*	43*
6	61.31	4.6	10*	64.55*	4.8*	23*
7	79.41*	2.9*	76*	84.77*	2.8*	74*
8	81.60*	3.6*	69*	82.22*	3.6*	73*
9	67.74	4.1	37*	72.78*	4.5*	64*
10	62.35	4.6	9*	76.09*	5.2*	40*
11	60.84	3.5	0	56.81	1.8	0
12	58.44	1.6	0	61.37	2.8	6*
13	76.45*	4.1*	63*	72.88*	4.1*	51*
14	72.14*	3.0*	53*	78.50*	3.1*	63*
15	61.21	3.1	0	64.25	3.9	5*
16	59.28	4.5	0	63.05	1.8	0
M	66.34	3.61	23.19	69.60	3.51	33.69
SE	1.96	0.19	7.18	2.03	0.28	28.41

Notes. Acc=maximum cross-validated classification accuracy (%); Time=time of Acc (seconds following offset of auditory cue); #TP=number of time points for which statistically reliable classification results were obtained; *M*=mean; *SE*=standard error of the mean.

*p<.05, with False Discovery Rate correction for multiple comparisons

Appendix D: Clinical behavioural data for the patients in Chapter 4.

Coma Recovery Scale-Revised scores for each patient immediately prior to the experimental assessments with electroencephalography and functional magnetic resonance imaging.

ID	CRS-R Sub-scores at EEG assessment							CRS-R Sub-scores at fMRI assessment						
	Test	**Auditory**	**Visual**	**Motor**	**Oromotor**	**Comm**	**Arousal**	**Task**	**Auditory**	**Visual**	**Motor**	**Oromotor**	**Comm**	**Arousal**
VS1	1	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim	Attention	1-Startle	1-Startle	0-None	1-Reflexive	0-None	2-Eye open w/out stim
								Imagery	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim
VS2	1	1-Startle	0-None	1-Abnormal posturing	1-Reflexive	0-None	1-Eye open w/ stim	Attention	1-Startle	0-None	1-Abnormal posturing	1-Reflexive	0-None	1-Eye open w/ stim
								Imagery	1-Startle	1-Startle	0-None	1-Reflexive	0-None	1-Eye open w/ stim
VS3	1	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim	Both	1-Startle	1-Startle	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim
VS4	1	2-Localization	1-Startle	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim	*(fMRI assessments conducted only at EEG Session 2)*						
	2	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim	Imagery	1-Startle	1-Startle	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim
								Attention	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim
VS5	1	1-Startle	0-None	1-Abnormal posturing	1-Reflexive	0-None	1-Eye open w/ stim	Attention	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim
								Imagery	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim

ID	CRS-R Sub-scores at EEG assessment							CRS-R Sub-scores at fMRI assessment						
	Test	Auditory	Visual	Motor	Oromotor	Comm	Arousal	Task	Auditory	Visual	Motor	Oromotor	Comm	Arousal
VS6	1	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim	Both	0-None	1-Startle	0-None	0-None	0-None	2-Eye open w/out stim
	2	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim	Both	0-None	0-None	0-None	0-None	0-None	2-Eye open w/out stim
VS7	1	1-Startle	0-None	1-Abnormal posturing	1-Reflexive	0-None	2-Eye open w/out stim	Imagery	1-Startle	1-Startle	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim
								Attention	1-Startle	0-None	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim
MCS1	1	1-Startle	1-Startle	1-Abnormal posturing	1-Reflexive	0-None	1-Eye open w/ stim	Both	1-Startle	3-Pursuit	1-Abnormal posturing	1-Reflexive	0-None	1-Eye open w/ stim
MCS2	1	1-Startle	3-Pursuit	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim	Both	1-Startle	3-Pursuit	4-Object manipulation	1-Reflexive	0-None	1-Eye open w/ stim
MCS3	1	3-Reproducible movement to command	3-Pursuit	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim	Imagery	2-Localization	3-Pursuit	2-Flexion withdrawal	1-Reflexive	0-None	2-Eye open w/out stim
								Attention	1-Startle	3-Pursuit	2-Flexion withdrawal	1-Reflexive	0-None	1-Eye open w/ stim
	2	3-Reproducible movement to command	3-Pursuit	2-Flexion withdrawal	2-Vocalization	0-None	2-Eye open w/out stim	*(fMRI assessments conducted once 7.5 months prior to EEG Session 1)*						
MCS4	1	1-Startle	3-Pursuit	1-Abnormal posturing	1-Reflexive	0-None	2-Eye open w/out stim	Imagery	1-Startle	3-Pursuit	1-Abnormal posturing	1-Reflexive	0-None	2-Eye open w/out stim
								Attention	2-Localization	3-Pursuit	1-Abnormal posturing	1-Reflexive	0-None	2-Eye open w/out stim
EMCS1	1	4-Consistent movement to command	5-Object recognition	6-Functional object use	2-Vocalization	2-Accurate, Functional	3-Attention	Imagery	4-Consistent movement to command	5-Object recognition	6-Functional object use	2-Vocalization	2-Accurate, Functional	3-Attention
								Attention	4-Consistent movement to command	4-Object localization	4-Object manipulation	1-Reflexive	1-Non-Functional: Intentional	1-Eye open w/ stim

ID	CRS-R Sub-scores at EEG assessment							CRS-R Sub-scores at fMRI assessment						
	Test	**Auditory**	**Visual**	**Motor**	**Oromotor**	**Comm**	**Arousal**	**Task**	**Auditory**	**Visual**	**Motor**	**Oromotor**	**Comm**	**Arousal**
	2	*(Not assessed)*[a]						*(fMRI assessments conducted once 1.5 months prior to EEG Session 1)*						
EMCS2	1	4-Consistent movement to command	5-Object recognition	6-Functional object use	3-Intelligible verbalization	2-Accurate, Functional	3-Attention	Imagery	4-Consistent movement to command	5-Object recognition	5-Automatic response	0-None	2-Accurate, Functional	3-Attention
								Attention	4-Consistent movement to command	5-Object recognition	5-Automatic response	3-Intelligible verbalization	2-Accurate, Functional	3-Attention
LIS1	1	4-Consistent movement to command	5-Object recognition	0-None	1-Reflexive	2-Accurate, Functional	3-Attention	Both	4-Consistent movement to command	5-Object recognition	0-None	1-Reflexive	2-Accurate, Functional	3-Attention

Notes. CRS-R=Coma Recovery Scale-Revised (Kalmar & Giacino, 2005); EEG=electroencephalography; fMRI=functional magnetic resonance imaging; Comm=communication; w/=with; stim=stimulation; VS=Vegetative State; MCS=Minimally Conscious State; EMCS=emergent from a Minimally Conscious State; LIS=Locked-in Syndrome.

[a]Patient EMCS1 was not assessed with the CRS-R at her replication session. However, she could communicate using an arm movement.

Curriculum Vitae

Post-Secondary Education

PhD (Psychology–Behavioural and Cognitive Neuroscience) In Progress
Department of Psychology, Western University, London, CAN

BSc (Honours, Neuroscience–Neuropsychology) 2012
Centre for Neuroscience, Brock University, St. Catharines, CAN

Publications

Norton, L., **Gibson, R. M.**, Gofton, T., Benson, C., Dhanani, S., Shemie, S. D., Hornby, L., Ward, R., & Young, G. B. (2017). Electroencephalographic recordings during withdrawal of life sustaining therapy. *Canadian Journal of Neurological Sciences*, *44*, 139–145. http://dx.doi.org/10.1017/cjn.2016.309.

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Awards

NSERC Vanier Canada Graduate Scholarship	2014–17
NSERC Michael Smith Foreign Study Supplement	2015
Ontario Graduate Scholarship with Distinction – Doctoral	2013–14
NSERC Canada Graduate Scholarship – Masters	2012–13
Distinguished Graduating Student Award – Neuroscience	2012
Residents Committed to Excellence Award	2012
Scheaffe Hall Award	2012
Alumni Honours Scholarship	2011
Bean and Bean Becker Scholarship in Mathematics and Science	2011
NSERC Undergraduate Student Research Award	2011
Brock University Library Research Award	2011
Brock University Undergraduate Psychological Research Prize	2011
NSERC Undergraduate Student Research Award	2010
Brock University Leaders Award	2008
Roy Cairns Scholarship	2008
Jon and May Ella Houghton Scholarship	2008
Marion and Ren Henderson Scholarship	2008
Brock University Entrance Scholarship	2008
Governor General’s Academic Medal – Bronze	2008