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Functional Magnetic Resonance Imaging as an Assessment Tool in Critically Ill Patients

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Abstract

Little is known about whether residual cognitive function occurs in the earliest stages of brain injury. The overarching goal of the work presented in this dissertation was to elucidate the role of functional neuroimaging in assessing brain activity in critically ill patients. The overall objective was addressed in the following four empirical chapters:

In Chapter 2, three versions of a hierarchically-designed auditory task were developed and their ability to detect various levels of auditory language processing was assessed in individual healthy participants. The same procedure was then applied in two acutely comatose patients.

In Chapter 3, a hierarchical auditory task was employed in a heterogeneous cohort of acutely comatose patients. The results revealed that the level of auditory processing in coma may be predictive of subsequent functional recovery.

In Chapter 4, two mental imagery paradigms were utilized to assess covert command-following in coma. The findings demonstrate, for the first time, preserved awareness in an acutely comatose patient.

In Chapter 5, functional neuroimaging techniques were used for covert communication with two completely locked-in, critically ill patients. The results suggest that this methodology could be used as an augmentative communication tool to allow patients to be involved in their own medical decision-making.

Taken together, the proceeding chapters of this work demonstrate that functional neuroimaging can detect preserved cognitive functions in some acutely comatose patients, which has both diagnostic and prognostic relevance. Moreover, these techniques may be extended even further to be used as a communication tool in critically ill patients.

Keywords

Coma, functional magnetic resonance imaging, prognosis, diagnosis, disorders of consciousness

Co-Authorship Statement

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The chapters of this dissertation are manuscripts that have been prepared for publication in scientific journals. The chapters describe collaborative research projects where Loretta Norton is the primary author for all chapters and main contributor to all aspects of the research studies within, including: conceptualization and design, data collection, data analysis, interpretation of findings, and drafting of the articles. Dr. Jonathan Peelle provided advice for the development of the acoustic stimuli, conceptual design, a technical assistance with fMRI analysis in Chapters 2 and 3. Dr. Davinia Fernandez-Espejo made substantial contributions in the pre-processing and analysis of healthy control data presented in Chapter 4. Dr. Teneille Gofton, Dr. Bryan Young, Dr. Eyad Althenayan, and Dr. Derek Debicki participated in the recruitment of participants, were in charge of the medical safety of participants in the study and responsible for managing any serious adverse events, and contributed to the interpretation of study findings. Dr. Adrian Owen supervised all studies from conception and design, to the acquisition of data, and the analysis and interpretation of results. Dr. Owen also contributed to the critical revisions of the manuscripts for intellectual content.

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List of Abbreviations

AG: angular gyrus

AIE: anoxic-ischemic encephalopathy

ARAS: ascending reticular activating system

BOLD: blood-oxygen-level dependent

EEG: electroencephalography

FDR: false discovery rate

fMRI: functional magnetic resonance imaging

fNIRS: functional near-infrared spectroscopy

GBS: Guillain-Barré syndrome

GCS: Glasgow Coma Scale

GOS: Glasgow Outcome Scale

ICU: intensive care unit

IFG: inferior frontal gyrus

MCS: minimally conscious state

MTG: middle temporal gyrus

OPJ: occipito-parietal junction

ROI: region-of-interest

SCN: signal correlated noise

STG: superior temporal gyrus

TBI: traumatic brain injury

VS: vegetative state

Chapter 1

1.1 What is coma?

Coma is defined as a state of unarousable unconsciousness (Young, 2009), in which, arousal and awareness, the two physiological mechanisms that regulate conscious behaviour, are absent. The comatose state arises as a result of a severe brain injury that causes a failure of the ascending reticular activating system (ARAS), which is a series of neural circuits projecting from the brainstem to the thalamus and the cerebral cortex (Liversedge & Hirsch, 2010). The ARAS supports arousal, and damage to the ARAS causes the inability to maintain arousal and wakeful periods. Arousal is thought to mediate awareness (Young, 2009). Simply, arousal must be intact for the conscious perception of both internal awareness and external awareness. Thus, when damage to the ARAS is significant enough to results in the absence of arousal and awareness, an individual is said to be in a comatose state.

Coma can be difficult to characterize as it lies upon a spectrum of altered states of consciousness, and variations in clinical presentations may fall within the range where coma is indicated. Plum and Posner (2007) operationally define coma as: “a state of unresponsiveness in which the patient lies with eyes closed and cannot be aroused to respond appropriately to stimuli even with vigorous stimulation. The patient may grimace in response to painful stimuli and limbs may demonstrate stereotyped withdrawal responses, but the patient does not make localizing responses or discrete defensive movements” (Posner, Saper, Schiff, & Plum, 2007). Alternatively, Wijdicks (2008), defines a comatose patient as “a completely unaware patient with, at best, only eye opening with pain or eyes opening with no tracking or fixation, the presence of withdrawal to a noxious stimulus, or the presence or reflex motor movements. Brainstem reflexes can be intact or variable absent.” Importantly, coma should not be conceptualized as a single state but rather as a continuum (Fisher, 1969). Established coma scales are useful for accurately characterizing the depth of coma. A coma scale is a practical tool that allows for the quantification and standardization of important findings from a neurologic examination.

The most commonly used coma scale is the Glasgow Coma Scale (GCS). Developed by Jennett and Teasdale in 1974, the GCS is a scale that ranges from three (“deep unconsciousness”) to fifteen (“fully alert and oriented”). The GCS assesses patients in three domains: motor, verbal, and eye opening responses (Teasdale & Jennett, 1974). The patient’s best response on each domain is summed with the other domains to render a score (see Table 1.1). A GCS score of thirteen or higher indicates mild brain injury, nine to twelve indicates a moderate brain injury, and eight or less indicates a severe brain injury has occurred. A score of eight or less is often used as the operational definition of coma in research studies (Teasdale et al., 2014).

Table 1.1. Glasgow Coma Scale

Eye Response	**Sub-Score**
Eyes open spontaneously	4
Eye opening to verbal command	3
Eye opening to pain	2
No eye opening	1
Motor Response	**Sub-Score**
Obeys commands	6
Localizing pain	5
Withdrawal form pain	4
Flexion response	3
Extension response	2
No response	1
Verbal Response	**Sub-Score**
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Total	

While the GCS has become universally adopted worldwide in emergency rooms and intensive care units (ICUs) to assess any patient with a decreased level of consciousness (Teasdale et al., 2014), there are some known limitations of the scale. One such limitation is its reduced sensitivity in scoring the verbal domain in endrotracheally intubated patients, in which patients who otherwise might vocalize are unable to do so while intubated. Additionally, the GCS does not assess brainstem function or respiratory patterns. Other validated scales have been introduced to provide more neurological detail, such as the Full Outline of Unresponsiveness Score (Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005). Despite other scoring systems demonstrating superior neurological detail, the GCS remains the most popular coma assessment tool.

1.2 Causes of Coma

Structural brain lesions and metabolic disturbances are the two broad categories of injury that can produce coma. Structural brain lesions result from direct damage of brain tissue from either traumatic or non-traumatic origins. Metabolic coma frequently results from anoxic-ischemic encephalopathy following cardiac arrest, infection, or toxicity. Table 1.2 lists the common causes of coma.

Table 1.2 Common causes of coma. Adapted from Posner et al., 2007; Young, 2009.

Causes of Coma	Examples
Structural	
	hematomas
	hemorrhage
	tumor
	infarct
	diffuse axonal injury
Deprivation of oxygen, metabolic cofactors	
	hypoxia
	ischemia
	hypoglycemia
	cofactor deficiency
Toxicity of endogenous products	
	due to organ failure
	systemic diseases
	electrolyte disturbances
Toxicity of exogenous poisons	
	drug overdoses
Infection	
	meningitis
	encephalitis
Disordered temperature regulation	
	hyperthermia
	hypothermia
Seizure Disorders	
	status epilepticus

1.3 Differential Diagnosis of Coma

Coma can be mimicked by psychogenic unresponsiveness, the locked-in syndrome, and severe polyneuropathies. Each of these neurological conditions requires specific courses of treatment, and thus, differential diagnosis of these conditions has serious implications for appropriate management. Various methods of physical examination, patient history, and neuroimaging are required in order to properly differentiate among these disorders (Moore & Wijdicks, 2013).

Psychogenic unresponsiveness is a rare disorder in which patients appear behaviorally unaware but their unresponsiveness is psychogenic in origin and is not a result of injury to the brain. Behavioural features upon stimulation are largely confirmatory of "pseudocoma" (Young, 2009).

Patients suffering from locked-in syndrome are conscious but appear comatose at the bedside as they are unable to respond to stimuli due to paralysis of all limbs and paralysis of lower cranial nerves, termed anarthria, which affects the tongue, palate, jaw, and lower facial muscles. The locked-in syndrome is typically caused by a ventral pontine insult (Smith & Delargy, 2005). In classic (or typical) locked-in syndrome, the midbrain tectum is spared permitting vertical gaze and upper eyelid movement. Augmentative communication devices that decode eye movements and eye blinks can then be used to establish communication with the patient. However, in complete (or total/atypical) locked-in syndrome patients have total immobility and inability to communicate including absence of eye movements leaving them in a complete de-efferented state. Structural neuroimaging for lesion identification and electroencephalography (EEG), which can determine normal awake rhythms, can differentiate these patients from comatose patients (Young, 2009).

Polyneuropathies, such as severe Guillain-Barré syndrome, and progressive motor neuron diseases, such as end-stage amyotrophic lateral sclerosis, can also mimic coma. These patients have intact consciousness but suffer from total paralysis and de-efferentation. In severe GBS, patients may lose all brainstem reflexes, including pupillary reflexes, mimicking brain death (Friedman, Lee, Wherrett, Ashby, & Carpenter, 2003). Previous medical history of progressive muscle weakness and EEG can differentiate these patients from comatose patients (Bauer, Gerstenbrand, & Rumpl, 1979).

1.4 Outcome following Coma

Coma is not permanent, but rather a transitional state lasting between 2-4 weeks (Laureys, Owen, & Schiff, 2004). Following coma, patients may succumb to their injury, recover consciousness with or without disability, or develop a chronic disorder of consciousness. The major classifications of outcome are shown in Figure 1.1.

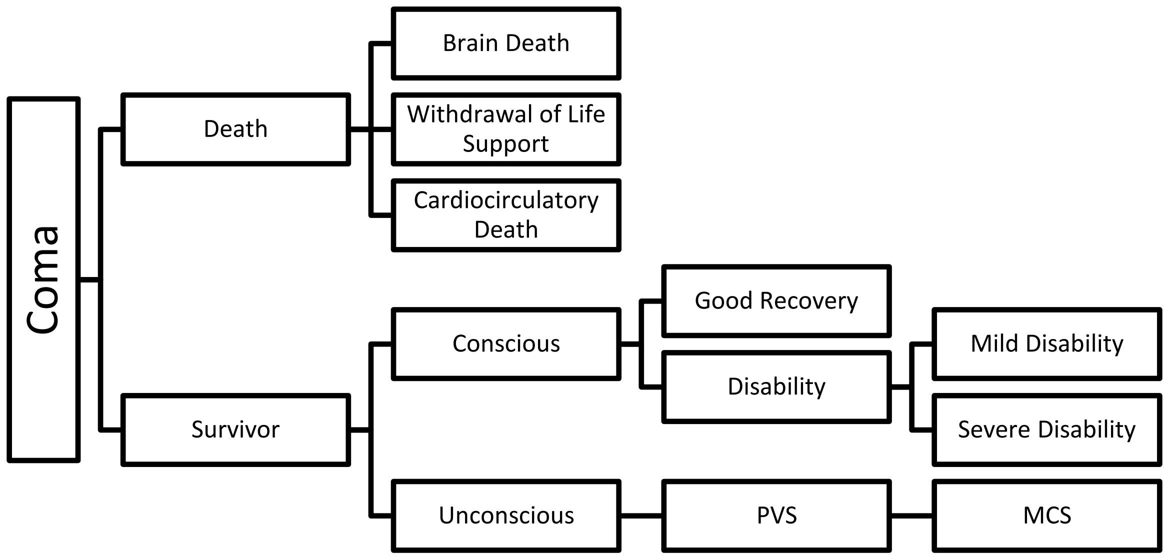

Figure 1.1. The main classifications of outcome following acute coma. PVS= persistent vegetative state, MCS = minimally conscious state. Modified from Wijdicks, 2008.

The most severe brain injuries lead to brain death, defined as the irreversible loss of all functions of the entire brain (Wijdicks, Varelas, Gronseth, & Greer, 2010). Brain death is confirmed through the absence of brainstem reflexes, the lack of responsiveness to stimuli, and apnea (Wijdicks et al., 2010). However, only a small proportion of comatose patients progress to brain death. More commonly, death results from the withdrawal of life sustaining therapies in ICU patients, as many brain injuries prevent meaningful neurological recovery but are not significant enough to result in brain death (Mark, Rayner, Lee, & Curtis, 2015).

Comatose survivors who remain unconscious progress to a chronic disorder of consciousness, such as the vegetative state (VS) or minimally conscious state (MCS). A transition from coma to VS usually occurs within 2-4 weeks following injury (Laureys et al., 2004). VS patients are different from comatose patients as they have recovered brainstem functions including the ability to breathe without the assistance of mechanical ventilation. Moreover, VS patients also have regained arousal, characterized by the return of sleep and wake cycles. Behaviorally, VS patients will open their eyes spontaneously for periods of time throughout the day (Jennett & Plum, 1972). While VS patients have regained wakefulness it is generally assumed that they maintain a lack of awareness of themselves and their environment. The Multi-Society Task Force on PVS (1994) has described the criteria for a diagnosis of vegetative state which includes: no evidence of awareness of self or environment and incapable of interactions with others; no evidence of sustained, reproducible, purposeful, or voluntary behavioural responses to external stimuli (visual, auditory, tactile, or noxious); no evidence of language comprehension or expression; bowel and bladder incontinence; present sleep-wake cycles; preserved autonomic function (including blood pressure, respiratory effort, and heart rate); and mostly preserved cranial nerve reflexes. Patients who remain in a vegetative state for more than 1 month are diagnosed as being in a persistent vegetative state (PVS) (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1995). Patients may further transition to a minimally conscious state (MCS) where they have minimal measureable evidence of awareness, which can be inconsistent at times (Bernat, 2006). The criteria for the diagnosis of MCS includes one or more of the following behaviors: following simple commands, verbalizing or gesturing yes/no responses, intelligible verbalizations, or observable purposeful behaviour (Giacino et al., 2002).

Comatose patients may either bypass these states of VS and MSC to regain full awareness, remain in a chronic disorder of consciousness, or progress through these states to recover consciousness after either a short or extended period of time.

Coma is compared with other states of unresponsiveness in Table 1.3.

Table 1.3 Characteristics of coma and other states of unresponsiveness. Adapted from The Multi-Society Task Force on PVS., 1994; Young, Ropper, & Bolten, 1998.

	Brain Death	Coma	Persistent Vegetative State (PVS)	Minimally Conscious State (MCS)	Locked-In Syndrome (including polyneuropathies)
Clinical Features					
Motor Function	None or only reflexive spinal movements	No purposeful movements	No purposeful movements	Variable with purposeful movements	Quadriplegia, bulbar/pseudobulbar palsy
Respiratory Function	Absent	Depressed, variable	Intact	Intact	Intact breathing in traditional LIS; Absent in severe polyneuropathies
EEG Activity	Electrocerebral Silence	Variable, dependent on severity, topography and etiology	Suppressed or slow	Non-specific slowing	Normal
Evoked Potentials	Absent	BAER variable; cortical ERPs often absent	BAER preserved; cortical ERPs variable	BAER preserved; cortical ERPs often preserved	BAER variable; cortical ERPs normal
Metabolism (PET)	Absent cortical metabolism	Resting <50%	Resting <50%	Reduced	Normal
Components of Consciousness					
Arousal	-	-	+	+	+
Awareness	-	-	-	+	+
Attention	-	-	-	r	+
Working Memory	-	-	-	-	+
Perception	-	-	-	r	+
Long-term memory	-	-	-	-	+
Motivation	-	-	-	-	+
Cognition	-	-	-	-	+
Prognosis for Neurological Recovery	No recovery	Variable, transitional state of 2-4 weeks	Variable	Variable	* Not a disorder of consciousness

+ = present; - = absent, r= reduced but present

1.5 Prognosis in Coma

Functional recovery following coma largely depends on the etiology of the injury that caused the comatose state. Most medical literature regarding prognostication in coma comes from two of the largest categories that produce coma: traumatic brain injury (TBI) and anoxic-ischemic encephalopathy (AIE) following cardiac arrest. Both etiologies have high mortality rates, ranging from 40-50% in TBI (Masson et al., 2001) and 54-88% in AIE (Booth, Boone, & Tomlinson, 2004). Of those who survive, more than half have permanent brain damage (Stiell et al., 2011; Young, 2009). In contrast, there are some survivors who go on to make a good recovery with no or minimal cognitive impairments (Howard, 2014). Thus, prediction of neurological outcome is essential in the management of the comatose patient.

Studies examining survival often use simplistic outcome scales to determine the level of functional recovery. The Glasgow Outcome Scale (GOS), developed by Jennett and Bond (1975), is the most widely used objective assessment tool for assessing functional outcome following severe brain injury. The GOS is a five-point scale where outcome is classified within one of five distinct levels: death, persistent vegetative state, severe disability, moderate disability, and good recovery (see Table 1.4).

Table 1.4. The Glasgow Outcome Scale (GOS). From Jennett and Bond, 1975.

Score	Classification	Description
1	Death	
2	Persistent vegetative state	Patient exhibits no obvious cortical function.
3	Severe disability	Conscious but disabled. Patient depends upon others for daily support due to mental or physical disability or both.
4	Moderate disability	Disabled but independent. Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	Good recovery	Resumption of normal activities even though there may be minor neurological or psychological deficits.

Current prognostication tools focus on the identification of poor outcome in coma patients, where a patient will not improve more than persistent vegetative state or severe disability requiring full nursing care. An indication of poor outcome leads to a consideration to withdraw life-sustaining therapies, as it is commonly thought that individuals would not choose to live in such a disabled state. Current prognostic indicators of poor outcome include: neurological examination, structural neuroimaging, electrophysiological testing (EEG and evoked potentials), and biomarkers. These prognostic tests have very low false positive rates indicating a great degree of specificity for predicting those that will have a poor outcome. Table 1.5 summarizes the current indicators of poor prognosis in AIE (Sandroni et al., 2013) and TBI (Stevens & Sutter, 2013) and the associated false positive rates.

Table 1.5 Prognostic markers in the assessment of poor outcome in TBI and AIE coma. Adapted from Sandroni et al., 2013; Stevens & Sutter, 2013.

	TBI	FPR for poor outcome	AIE	FPR for poor outcome
Neurological Examination	Myoclonus, unreactive pupils and absent corneal reflexes	0-11%	Combination of absent pupillary light reflex, corneal reflex and motor response no better than extension after rewarming	0-8%
Structural Neuroimaging	CT: decreased grey-white matter differentiation	0%	CT: decreased grey-white matter differentiation	0%
	MRI: decreased whole brain Apparent Diffusion Coefficient	0-23%	MRI: diffuse ischemic lesions (cortex + deep grey matter) 5 days	0%
EEG	unreactive background, bust-suppression, epileptiform discharges	0-9%	Non-reactive EEG background after rewarming	0-3%
Evoked Potentials	Bilaterally absent SSEP N20 at 3 days	0-3%	Bilateral absence of SSEP N20 waveform during hypothermia or after rewarming	0-4%
Serum	NSE above 33	4-29%	NSE above 33 mcg/L at 48 h	0%

biomarkers	mcg/L 0-3 days

Importantly, while current prognostic markers have a high degree of specificity, they lack sensitivity. When indicators of poor prognosis are absent, a patient is thought to have an indeterminate outcome. Unfortunately, there are currently no established prognostic indicators for positive outcome. Thus novel prognostic indicators that can improve the prediction of positive outcome are urgently required.

1.6 Functional Neuroimaging in Chronic Disorders of Consciousness

Functional neuroimaging techniques used for measuring and mapping brain activity may offer new ways for improving the diagnostic, prognostic, and therapeutic management of patients who suffer from disorders of consciousness.

Both positron emission tomography and functional magnetic resonance imaging (fMRI) have been used to passively assess the integrity of basic sensory, perceptual, and higher-order cognitive abilities in chronic disorders of consciousness. Such research has found cortical activation to auditory (Boly et al., 2004; Coleman et al., 2007; Fernández-Espejo et al., 2008; Laureys et al., 2000; Owen et al., 2002; Schiff et al., 2002), somatosensory (Boly et al., 2008; Laureys et al., 2002), visual (Giacino, Hirsch, Schiff, & Laureys, 2006; Menon et al., 1998), and emotional stimuli (Bekinschtein et al., 2004) in a small proportion of VS patients. These passive tasks indicate that some VS patients "retain preserved islands of residual cognitive function"(Schiff et al., 2002).

Importantly, such passive paradigms may have prognostic value. Findings of atypical activation of higher-order integrative cortical areas to external stimuli have been associated with improvements in functional recovery. A retrospective review of 48 case series' on VS patients found that activation in higher-order association cortices to a variety of external stimuli predicted recovery of consciousness with a 93% specificity and 69% sensitivity (Di, Boly, Weng, Ledoux, & Laureys, 2008). Similarly, neural activation to higher-level language processing in VS has been found to be strongly correlated with increased functional recovery 6 months following imaging (Coleman et al., 2009). Recently, higher-order activation to thermal stimulation has also been shown to correlate with favorable outcomes in VS patients (Li et al., 2014). However, while such passive fMRI tasks may be useful for the prediction of recovery they do not allow for the ability to determine the presence of conscious awareness.

Promisingly, Owen et al., (2006) designed two ‘active’ fMRI paradigms to detect covert awareness in a vegetative state patient. In the first paradigm the patient was asked to imagine playing a game of tennis and in the second paradigm the patient was instructed to imagine navigating through her house. Significant neural activation was observed in the supplementary motor area for motor imagery and was seen in the parahippocampal gyrus, posterior parietal cortex, and lateral premotor cortex for the spatial navigation task. The spatial localization and extent of activation in both paradigms was not different to that of healthy volunteer responses (Boly et al., 2007), indicating that the patient was consciously aware, despite the clinical diagnosis of vegetative state. In a larger follow-up study, Monti et al., (2010) used the same mental imagery tasks in a cohort of VS patients and found that 4/23 (17%) VS patients could willfully modulate their brain activity to command. This result suggests that fMRI should be used in concert with current diagnostic tools to detect covert signs of awareness.

In a step forward, the mental imagery tasks have been adapted to allow binary communication with some nonresponsive patients. As both the motor and spatial navigation mental imagery tasks are known to produce spatially distinct patterns of activation, patients have been asked to perform one imagery task to indicate a ‘yes’ response and the alternate imagery task to indicate a ‘no’ response. The spatial localization of the neural activation allows researchers to decode the patient’s response to simple yes-or-no questions. Using this technique, Monti et al., (2010) reported on one VS patient who was able to answer five of six questions with 100% accuracy. In another case report of a VS patient, the fMRI communication technique was extended beyond evaluating responses that had factually-known answers to asking private internal knowledge, such as “are you in pain?” (Fernández-Espejo & Owen, 2013). Thus, establishing communication through fMRI allows otherwise non-responsive patients the ability to communicate in order to provide insights into their quality of life and clinical condition while potentially allowing them make decisions about their own medical care.

1.7 Functional Neuroimaging in Acute Disorders of Consciousness

While a significant amount of functional neuroimaging research has examined brain activity in chronic disorders of consciousness, very few studies have examined the use of fMRI in an acute ICU setting with critically ill patients, such as those in coma.

To date, four fMRI studies have been published in relation to prognostic evaluation in acutely comatose patients. In 2001, an fMRI study on a TBI comatose patient found intact sensory processing to sound, tactile, and visual stimuli (Moritz et al., 2001). Interestingly, the patient subsequently recovered cognitive and sensorimotor functions at 3 months, providing the first evidence that fMRI may be useful for prognostication in acute brain injury. Gofton et al., 2009 used a passive tactile paradigm in a group of AIE comatose patients and found that those who recovered consciousness had greater activation in primary somatosensory cortex in comparison to patients who succumbed to their injury. Our research group (Norton et al., 2012) and others (Koenig et al., 2014) have also used resting state fMRI and found that connectivity strength within the default mode network is associated with functional outcome in AIE coma patients. Taken together, these limited findings suggest that fMRI might be a useful prognostic tool. Covert consciousness and communication abilities have never been evaluated in acute critically ill patients.

1.8 Aims of the Current Studies

The utility of functional neuroimaging in the earliest stages of brain injury remains largely unknown. The aim of this thesis was to determine if fMRI paradigms can be used to provide new diagnostic and prognostic information for clinicians to aid in the management of critically ill patients.

In Chapter 2, our aim was to develop an fMRI paradigm that could be used to interrogate auditory processing in a hierarchical manner including lower-level sound perception, mid-level speech perception, and higher-order language comprehension in individual participants, including patients in the earliest stages of a brain injury. We hypothesized that we would be able to acquire reliable single-participant data in healthy individuals on a lower field strength 1.5T clinical scanner. Additionally, we applied the paradigm to two comatose patients in which we hypothesized that their level of auditory processing would be predictive of functional recovery.

Chapter 3 builds directly from the findings presented in Chapter 2, utilizing the same fMRI hierarchical auditory task to evaluate sound perception, speech perception, and language comprehension in a larger cohort of comatose patients. The goal of the study was to determine if the passive auditory task had prognostic utility in comatose patients. It was hypothesized that the level of auditory processing in individual patients would correlate with their subsequent functional recovery.

In Chapter 4, we used two mental imagery tasks in a group of comatose patients to determine if these patients can have covert signs of awareness, similar to findings in some vegetative state patients. We hypothesized that we would be able to map, for the first time, covert awareness in some patients who clinically appear to be comatose.

In Chapter 5, we used the fMRI mental imagery tasks described in Chapter 4 as a means to establish communication with two patients with severe Guillain-Barré syndrome, whose clinical conditions mimicked coma and brain death. In the chapter we described the utility of fMRI as a communication tool to assess the patients' clinical condition and mental status.

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Chapter 2

2 Single-Subject Reliability of fMRI Language Paradigms and Their Clinical Utility in Acute Coma

2.1 Introduction

Comatose patients lie with their eyes closed and do not respond appropriately to any stimulation (Posner et al., 2007) as coma is an acute condition of unarousable unconsciousness (Young, 2009). Importantly, coma is transient in nature and does not usually last more than 30 days (Posner et al., 2007) at which point a patient may have either succumbed to their injury, regained consciousness (with or without neurological deficits), or failed to make significant progress in their recovery and transitioned to a chronic disorder of consciousness such as the vegetative state (VS) or minimally conscious state (MCS).

A growing body of research using functional neuroimaging in VS and MCS patients has shown that some of these patients can still have intact speech processing (Coleman et al., 2009; Coleman et al., 2007; Fernández-Espejo et al., 2008; Owen et al., 2005), vision (Giacino et al., 2006; Owen et al., 2002), somatosensation and nociception (Boly et al., 2008; S. Laureys et al., 2002; Li et al., 2014), and executive functioning (Monti, Coleman, & Owen, 2009; Naci, Cusack, Anello, & Owen, 2014; Naci, Cusack, Jia, & Owen, 2013), including volitional ability and communication (Monti et al., 2010; Owen, Coleman, et al., 2006). All are undetectable through traditional bedside examination. The use of functional neuroimaging techniques has brought into question whether the standard clinical method for diagnosing unresponsiveness is adequate and suggests that there may be a high rate of misdiagnosis among these patients (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993; Schnakers et al., 2009). As a result, there have been calls to include validated and standardized functional neuroimaging techniques in the assessment and diagnoses of VS and MCS patients (Fernández-Espejo & Owen, 2013; Fins et al., 2008; Laureys & Schiff, 2012). However, it remains to be determined if functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) could also be a viable approach to assessment in *acute* disorders of consciousness such as coma. Various challenges would have to be overcome for this to be feasible in patients within the intensive care unit (ICU).

One problem is that many of the available fMRI paradigms have been validated in groups of healthy participants and not evaluated at the single-subject level. It is important to know how robust the fMRI activations are in individual healthy subjects before one can interpret findings in an individual patient, especially when those results may inform clinical practice and patient management. Mental imagery tasks have been shown to be highly robust and reliable in detecting covert command following at the single-subject level in healthy volunteers (Boly et al., 2007; Fernández-Espejo, Norton, & Owen, 2014), as the effect size is quite large. However, a challenge occurs for higher-order processes such as language comprehension which must be isolated by the subtraction of a baseline condition that controls for both sensory and perceptual processing of sound and speech, resulting in smaller effect sizes (Binder, Swanson, Hammeke, & Sabsevitz, 2008; Davis & Johnsrude, 2003; Uppenkamp, Johnsrude, Norris, Marslen-Wilson, & Patterson, 2006).

A second problem is that many of the existing fMRI paradigms have been conducted on 3 T magnets but, in the clinical setting, many hospitals are equipped with 1.5 T scanners. Therefore, before any paradigm can be used clinically, it has to be validated on healthy subjects at lower field strength to determine if the same blood-oxygen-level dependent (BOLD) signal sensitivity is observed. Mental imagery tasks demonstrate robust and reliable activation at both field strengths in individual participants (Fernández-Espejo et al., 2014), but this is yet to be established for higher-order language tasks.

A third problem is that the only patient group that has been studied to date are chronically stable patients who have regained wakefulness and brainstem function (The Multi-Society Task Force on PVS., 1994), including the ability to breathe without mechanical ventilation support. FMRI paradigms may not be viable in more acute conditions like coma, where patients may lack wakefulness and brainstem reflexes.

While there are numerous challenges to overcome, it is nonetheless important to pursue this line of investigation in acute coma, particularly because neuroimaging studies have found that residual brain function to external stimuli in VS and MCS can yield valuable prognostic information (Di et al., 2008). However, once a patient has emerged to a chronic disorder of consciousness, it is less likely that the result of any fMRI investigation would inform decisions about the continuation of life sustaining therapies, as the withdrawal of nutrition and hydration rarely occurs at that stage. On the other hand, if fMRI studies could be shown to have prognostic value in coma, this would make an important contribution to decision making, as discussions regarding continued aggressive life support versus a withdrawal of life sustaining therapies are often made during this acute window.

Our goal in this study was to develop an fMRI paradigm that could be used to assess various levels of auditory language processing, including sound perception, speech perception, and language comprehension in individual participants, including patients in the earliest stages of a brain injury. We developed and assessed the reliability of three versions of a hierarchically-designed auditory task to detect single-subject activation in healthy individuals and then tested whether this same procedure was viable in two acutely comatose patients. We hypothesized that we would be able to acquire reliable single-participant data on a 1.5 T clinical scanner in healthy individuals, as we have previously demonstrated that mental imagery tasks, used to detect covert command following, have high single subject reliability at 1.5T similar to findings at 3T (Fernández-Espejo et al., 2014). Furthermore, as fMRI is becoming more routine for clinical use, particularly in single-subject pre-surgical evaluation of language lateralization in cases of epilepsy foci resection (Szaflarski et al., 2017), we predicted we would detect various levels of auditory processing in individual healthy volunteers using a lower field strength clinical scanner. Additionally, based on previous work in VS and MCS patients that found that the level of auditory processing strongly correlated with the patient’s functional recovery (Coleman et al., 2009), we hypothesized that the level of auditory processing would be predictive of outcome in two comatose patients.

2.2 Methods

2.2.1 Participants

Fourteen healthy right-handed native English speakers (M_{age}: 25.6 ± 6.4 years, 7 males) with no known neurological or psychiatric disease took part in the study. All had normal hearing by self-report. All participants provided their written informed consent and were compensated for their participation. Ethical approval for the research study was obtained by the Health Sciences Research Ethics Board of Western University and all study procedures were performed in accordance with relevant guidelines and regulations.

2.2.1.1 Comatose Patients

Two comatose patients participated in the study and written informed consent was obtained from their substitute decisions makers. The fMRI findings were not used in any clinical decision-making for either patient.

Patient 1 was a right-handed, native English speaking, 62 year old male, with normal hearing history based on report from the patient's family. He was admitted to ICU after a witnessed in-hospital cardiac arrest following a lengthy stay for a liver transplant that was complicated by intra-abdominal sepsis. He received 10 minutes of CPR followed by two doses of epinephrine and, following the return of spontaneous circulation, he underwent therapeutic hypothermia. Upon normothermia and removal of sedation the patient had positive pupillary light reflexes, but absent corneal, cough, and gag reflexes. Three days following injury, an EEG recording appeared suppressed. An MRI was performed four days after injury when the patient had a Glasgow Coma Scale (GCS) score of 3T (1E, 1V, 1M). The structural MRI sequences showed widespread diffusion trace brightness in the cerebellum, basal ganglia, caudate, thalami, and frontoparietal cortices consistent with hypoxic ischemic injury. The patient's prognosis was thought to be very poor for any meaningful recovery and a decision was made with family to remove life support measures.

Patient 2 was a right-handed, native English speaking, 56 year old male, with normal hearing history based on report from the patient's family. He was admitted to ICU after a witnessed out-of-hospital cardiac arrest. He received immediate cardiopulmonary resuscitation followed by five rounds of defibrillation and received multiple doses of epinephrine at the scene. The patient underwent therapeutic hypothermia following return of spontaneous circulation. The patient remained deeply comatose once normothermia was re-established but had intact brainstem responses with positive pupillary light reflexes, cough, gag, and vestibilo-ocular reflexes. An EEG, performed three days following injury, showed theta coma and generalized slowing of background that suggested a moderately severe encephalopathy with a lack of reactivity to auditory and painful stimuli on the EEG, thought to be an unfavourable prognostic factor. SSEPs were performed four days after injury and were bilaterally present. An MRI was also performed four days following when the patient had a GCS score of 3T (1E, 1V, 1M). The structural MRI sequences showed patchy diffusion trace brightness most notable along the frontal, occipital paramedian cortices, caudate nuclei, periventricular locations and posteromedial thalami. These findings were consistent with hypoxic ischemic injury. On the fifth day following injury, the patient had some spontaneous right arm and leg movement and spontaneous eye opening. The patient had subsequent improvement in awareness on Day 7 and could obey commands on Day 13. He was transferred to the medical ward 22 days following admission and still had some confusion that improved but did not completely resolve. He was then transferred to a brain injury unit at a rehabilitation hospital and made steady gains. He was able to return to work 5 months post injury. At a 6-month follow-up he had resumed his normal activity prior to admission and had made a good recovery with a Glasgow Outcome Scale (GOS) score of 5.

2.2.2 Hierarchical Auditory Paradigms

Three different versions of the auditory paradigm were developed to determine which one was the most suitable for addressing hierarchical auditory processing in individual participants, including sound perception, speech perception, and language processing. Each paradigm consisted of four different auditory conditions: silence, signal correlated noise (SCN), complex language and one of several language control conditions. Each paradigm was presented in the same interleaved block design where each condition was thirty seconds in length and repeated five times for a total of ten minutes (see Figure 2.1).

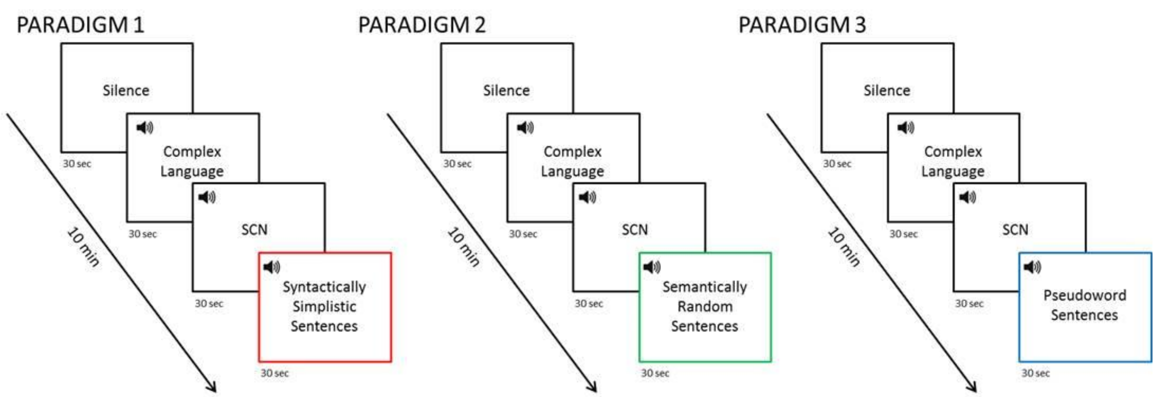

Figure 2.1. Design of the auditory fMRI paradigms. Each paradigm was identical with respect to three of the four conditions, silence, SCN, and complex language. Only the language control condition differed in each paradigm, where Paradigm 1 had syntactically simple sentences, Paradigm 2 had semantically meaningless sentences, and Paradigm 3 pseudoword sentences presented.

The three paradigms were identical with respect to three of the four conditions (silence, SCN, and complex language). Only the language control condition differed in each case. We did this to determine which one of three possible sets of stimuli was the most suitable baseline for the complex language condition; namely, the one that most robustly detected language comprehension at the single-subject level. All speech stimuli were recorded by a male native English speaker.

The complex language condition consisted of five linguistically complex short stories designed to maximally drive language processing. This was accomplished by using sentences that contained both subject-relative and object-relative embedded clauses within each short story. The use of embedded clauses within the narratives increased the complexity of the sentence structures, effectively making the stimuli more difficult to comprehend, and subsequently, more effortful for the listener, as they increased the demands on syntactic processing (Peelle, Troiani, Wingfield, & Grossman, 2010). We also manipulated the distance between the main clause noun phrase and its corresponding verb in order to increase working memory demands; again, this increased the complexity of the story and comprehension required greater effort on the part of the participant. Each sentence contained an average of 10 content words (nouns, verbs, adverbs, adjectives and negatives) with an average total length of 18 words per sentence (see Table 2.1 for examples).

Table 2.1. Example of speech stimuli.

Language Condition across all Paradigms	Complex Language	The woman that the man helped slammed the door after the mouse.
Paradigm 1 Language Control Condition	Syntactically simplistic sentences	That man has a dog.
Paradigm 2 Language Control Condition	Semantically random sentences	The human what the ran hemmed crammed the sore enter the mount.
Paradigm 3 Language Control Condition	Pseudoword sentences	Thi wesan frat thi han helved slanned thi woor auler thi moule.

Three variations of the language control condition were employed, with either less syntactic complexity within sentences than the complex language stimuli or sentences that lacked any semantics (see Table 2.1 for examples). In Paradigm 1, syntactically simple sentences were presented with an average of four words per sentence with the nouns and verbs spaced an average of two words apart. In Paradigm 2, each word within the complex language condition was replaced with a random English word (semantically random sentence condition). In Paradigm 3, each word within the complex language condition was replaced with a pseudoword, which is a non-word that has no meaning in the English lexicon, (pseudoword sentence condition). In Paradigm 2 and Paradigm 3, the words were matched to the original word target in the complex language condition according to subsyllabic structure and transition frequency through the use of a pseudoword generator (Keuleers & Brysbaert, 2010). The resulting sentences had no semantic relationship or grammatical structure but were read with sentence prosody.

The complex language condition was also used to generate an unintelligible signal-correlated noise condition (SCN) (Schroeder, 1968) which had the same amplitude envelope and spectral profile as complex language condition, but all spectral detail was replaced by noise. This condition provided a good contrast to the speech conditions as it contained a similar temporal pattern but lacked any linguistic information (Peelle, Eason, Schmitter, Schwarzbauer, & Davis, 2010; Rodd, Davis, & Johnsrude, 2005; Stoppelman, Harpaz, & Ben-Shachar, 2013).

Finally, the 'silence' condition consisted of five 30-second blocks where no stimuli were presented at all.

2.2.3 MRI acquisition

Imaging was performed on a 1.5 T General Electric Signa Excite MRI system (Fairfield, CT) at the University Hospital LHSC (London Health Sciences Centre, London, Canada). The functional paradigms used a T2*-weighted one-shot spiral-in sequence to obtain 240 volumes of 30 slices (TR = 2500ms, TE = 40ms, matrix size = 64 x 64, slice thickness = 5mm, in-plane resolution = 3.75mm x 3.75mm, flip angle 90°). A T1-weighted 3d-SPGR pulse sequence (TR = 9.2-10.2ms, TE = 4 ms, IT = 300, matrix size = 256 x 256, voxel size = 1.02 x 1.02 x 1.40 mm, flip angle = 10°) was also obtained. The auditory stimuli were presented using SuperLab 4.0 running on a Windows XP PC and delivered with noise-attenuated MRI-compatible headphones (Resonance Technology Inc.).

2.2.4 FMRI analysis

Image preprocessing and statistical analyses were conducted using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm). Preprocessing steps were identical for healthy control participants and the comatose patients. Briefly, data was manually AC-PC reoriented, functional images were realigned to help correct for motion, co-registered to the structural images, structural data was segmented, data was then normalized to the echo planar imaging template provided in SPM8, and smoothed using an 8mm FWHM Gaussian kernel. Single-subject fixed effect analysis was used for each participant. Based on the general linear model, regressors for each paradigm that corresponded to the presentation of silence, signal correlated noise, and the two speech conditions were created by convolving boxcar functions with the canonical hemodynamic response function. Movement parameters were included as covariates.

We assessed sound perception within each paradigm by comparing the haemodynamic responses of all auditory stimuli conditions (SCN, complex language, and language control condition) to the silent baseline condition in order to identify brain areas that were responsible for processing the acoustic properties of both speech and non-speech sounds. To identify areas solely responsible for speech-specific processing in each paradigm, we collapsed both speech conditions (complex language and language control condition) and contrasted them to the SCN condition. To identify the fMRI responses associated with language comprehension we contrasted the complex language condition to the language control condition within each paradigm. It is generally accepted that a difference in activity that places different demands on comprehension is a reasonable indicator that comprehension has occurred in absence of behavioural response (Davis & Johnsrude, 2003; Johnsrude, Davis, & Hervais-Adelman, 2005; Rodd et al., 2005).

At the group level, a one-sample t-test was performed across the 14 healthy participants to obtain the group pattern of activity associated with each contrast in each paradigm at the whole-brain level, using a cluster- defining voxelwise threshold of p <.001 (uncorrected), and whole-brain FDR-corrected for significance using cluster extent, p <.05.

At the single-subject level, functional activation was assessed using a region of interest (ROI) approach. ROIs were defined using Neurosynth, a large-scale meta-analytic database (Yarkoni, Poldrack, & Nichols, 2011), by utilizing the reverse statistical inference map that was preferentially related to the terms ‘sound’, ‘speech perception’ and ‘language comprehension’. Significant clusters were selected as ROIs from the derived maps if the z-score was greater than 7 and had a cluster size of more than 200 voxels (Figure 2.2).

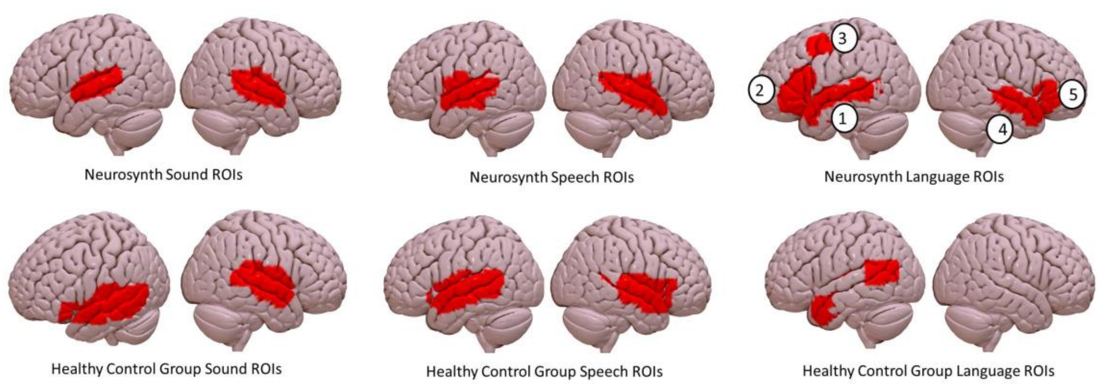

Figure 2.2. Regions-of-interest (ROIs) used. Top Panel - Neurosynth ROIs used for all three contrasts used in healthy participants. The sound perception ROIs included 2 clusters representing bilateral primary auditory cortex. The speech perception contrast ROIs included the bilateral STG. Five language-related ROIs were used for the language comprehension contrast which included left superior/middle temporal gyrus (1), left ventral inferior frontal gyrus (2), left middle frontal gyrus (3), right temporal pole (4), and right inferior gyrus (5). Bottom Panel – Healthy control group ROIs generated for all three contrasts used in patient participants. The sound perception contrast included 2 ROIs surrounding the primary auditory cortex bilaterally along the STG. The speech perception contrast ROIs included bilateral STG. The language-related ROI extended from the angular gyrus through the MTG.

For sound perception, clusters representing bilateral primary auditory cortex (peak coordinates: R=60,-24, 4; L=-48,-24, 8) were implemented as the ROIs. For the speech perception contrast we used two ROIs representing the anterior portion of the superior temporal gyrus (peak coordinates: R=64,-6,-4; L=-62,-8,0). For language comprehension, five language-related ROIs were used, which included left ventral inferior frontal gyrus (peak coordinates: -44,22,16), right temporal pole (peak coordinates: 50,8,-22), left posterior middle temporal gyrus (peak coordinates: -56,-46,6), right inferior gyrus (peak coordinates: 56,26,0), and left middle frontal gyrus (peak coordinates: -42,6,52). For the single-subject analysis, the statistical threshold was set at an uncorrected $p < .001$ because of a lower signal-to-noise ratio in comparison to group studies (Fadiga, 2007).

Additionally, we examined the lateralization for each contrast at the single subject level by calculating the laterality index (LI) through the use of the LI-toolbox (Wilke & Lidzba, 2007). Temporal lobe ROIs (as provided by the LI-toolbox) were used as the inclusive mask for the unthresholded individual t-maps for each contrast. We employed a bootstrap approach to calculate LI whereby a large amount of bootstrapped resamples are analyzed at different thresholds to produce the weighted mean LI (LI_w). The LI_w has the advantage of allowing LIs for higher t-thresholds to have a greater influence in the overall average LI for each contrast while controlling for outliers. LIs < -.2 were classified as left lateralized, LIs > +.2 right lateralized and LIs $\geq$ -.2 and $\leq$+.2 were bilateral.

2.2.4.1 Comatose Patient Analysis

Functional activation for the comatose patients was assessed by examining ROIs that showed significant activation in the same contrast in the healthy controls. For the sound and speech perception contrasts, ROIs were generated from the healthy control group analysis using a cluster- defining voxelwise threshold of p <.001 (uncorrected), and whole-brain FDR-corrected for significance using cluster extent, p <.05. These ROIs were then used to identify areas in the coma patients using a peak voxelwise threshold of

p <.001, uncorrected. For language processing, an ROI encompassing a portion of the left AG extending to the MTG was generated from the group analysis of Paradigm 3's language contrast (complex language > pseudoword sentences) by using a cluster-defining voxelwise threshold of p <.05 uncorrected, and a cluster extent of p <.05 (uncorrected), consistent with the procedure used by Coleman et al., 2007 in identifying language processing in chronic disorders of consciousness. This ROI was then used to identify areas in comatose patients using a peak voxelwise threshold of p <.001, uncorrected.

2.3 Results

Healthy participants listened to 3 different versions of a hierarchically designed auditory paradigm. Each paradigm consisted of four auditory conditions: silence, signal correlated noise (SCN), complex language, and a language control condition. Only the language control condition differed in each paradigm (Paradigm 1 used syntactically simple sentences, Paradigm 2 used semantically random sentences, and Paradigm 3 used pseudoword sentences). To assess sound perception within each paradigm we compared all auditory conditions to the silent baseline condition. To identify speech perception, we collapsed both speech conditions and contrasted them to the SCN condition. To identify the fMRI responses associated with language processing we contrasted the complex language condition to the language control condition within each paradigm (either syntactically simple sentences in Paradigm 1, or semantically random sentences in Paradigm 2, or pseudoword sentences in Paradigm 3).

2.3.1 Sound Perception

At the group level, the sound conditions in all 3 paradigms compared to rest elicited significant activation of the bilateral temporal lobes with peak activation in the primary auditory cortical regions of the superior temporal gyrus (STG) (see Figure 2.3).

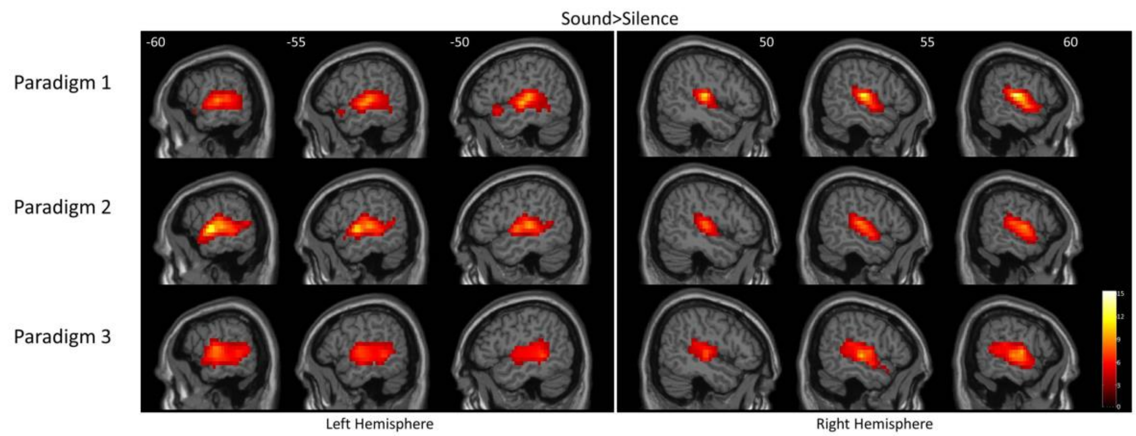

Figure 2.3. Whole-brain group analysis of healthy participants showing bilateral superior temporal gyrus activation to all sound stimuli compared to a silent baseline in each paradigm. Results are thresholded at *p* <.05, FDR-corrected for multiple comparisons with a threshold extent of 25 voxels and shown on a canonical single-subject T1 MRI image.

Using the region-of interest (ROI) approach at the single-subject level, all 14 healthy participants had primary auditory cortical activation to the sound perception contrast in Paradigm 1, although 2 participants (Participants 12 and 14) had only unilateral left auditory cortical activation. In Paradigm 2 all 14 participants demonstrated bilateral primary auditory activation while in Paradigm 3 bilateral activation was found in 13/14 participants. Single-subject activations are shown in Figure 2.4.

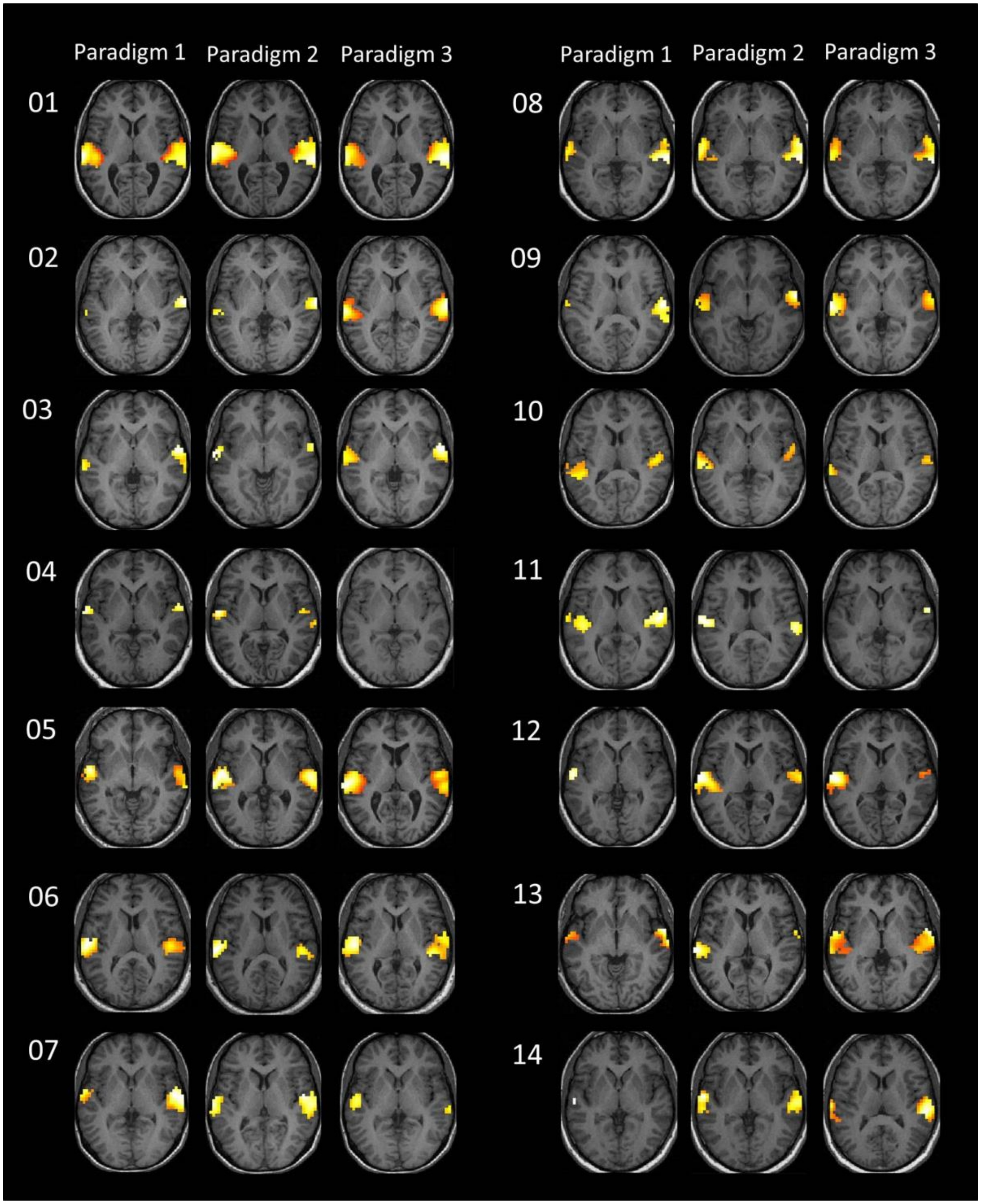

Figure 2.4. Single-subject level activation for all sound compared to silence. For each subject, slices with the peak activation are displayed on each individual's normalized T1 image. In Paradigm 1 and 2, primary auditory cortical activation was found in all participants while in Paradigm 3 activation was found in 13/14

participants. Results are thresholded at *p* <.001, uncorrected, masked inclusively by the sound perception Neurosynth ROI.

2.3.2 Speech Perception

At the group level, the speech conditions (complex language + language control condition) compared to SCN within each paradigm elicited significant bilateral activity in the anterior portion of the STG (Figure 2.5).

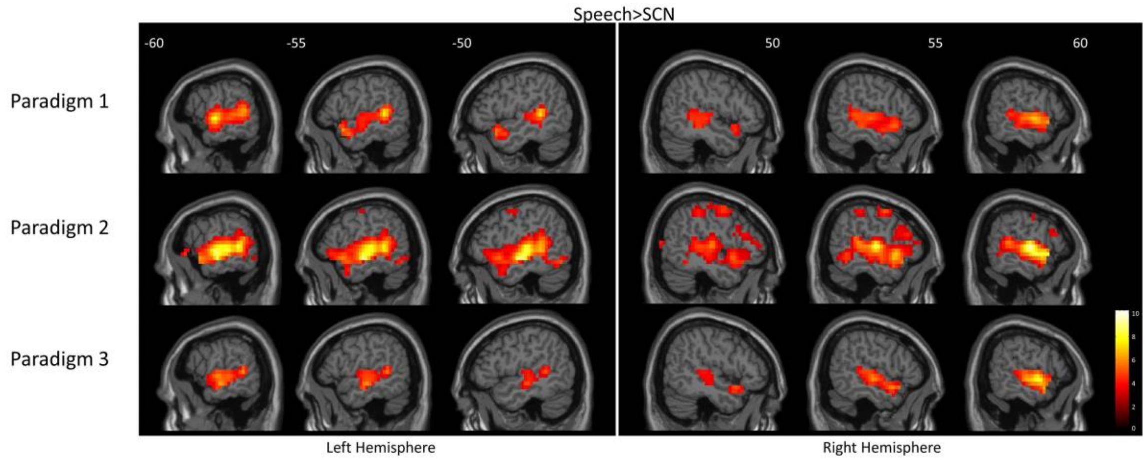

Figure 2.5. Whole-brain group analysis of healthy participants showing bilateral superior temporal gyrus activation to speech stimuli compared to signal correlated noise in each paradigm. Results are thresholded at p <.05, FDR-corrected for multiple comparisons with a threshold extent of 25 voxels and shown on a canonical single-subject T1 MRI image.

In Paradigm 2 all 14 healthy participants showed peak activation in the anterior STG to the speech perception contrast (speech conditions compared to SCN). In Paradigm 1 and Paradigm 3 bilateral activation was found in 13/14 participants. Participant 4 failed to show any significant activation in Paradigm 3 and Participant 14 failed to show any significant activation in Paradigm 1. Single-subject activations are shown in Figure 2.6.

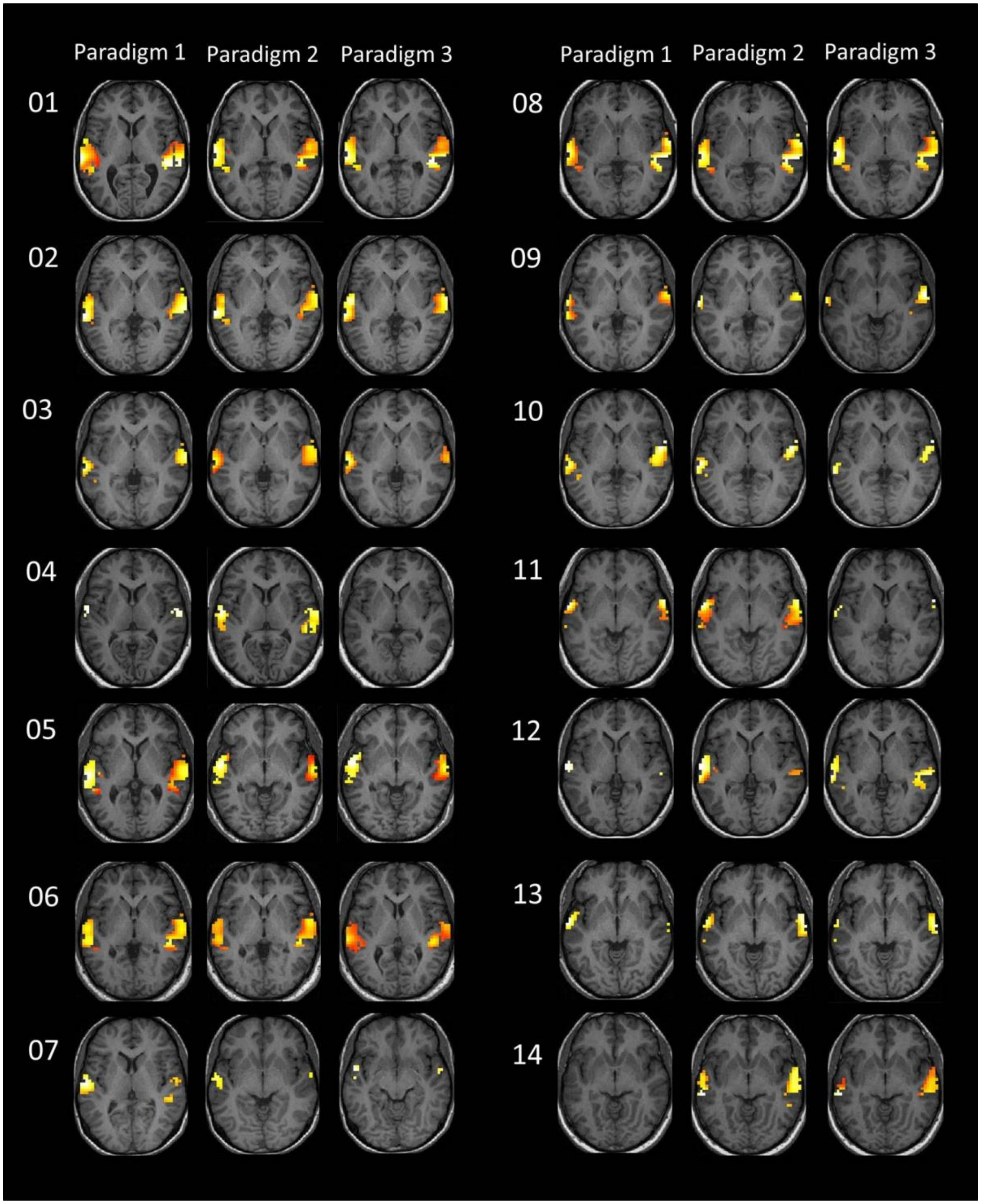

Figure 2.6. Single-subject level activation for speech compared to signal correlated noise. For each subject, slices with the peak activation are displayed on individual subjects' normalized T1 image. In Paradigm 2, bilateral anterior superior temporal gyrus activation was found in all participants while only 13/14 participants show

activation in Paradigm 1 or Paradigm 3. Participant 4 failed to show any significant activation in Paradigm 3 and Participant 14 failed to show any significant activation in Paradigm 1. Results are thresholded at p <.001, uncorrected, masked inclusively by the speech perception Neurosynth ROI.

2.3.3 Language Processing

In each paradigm, a different language control condition was used to determine which one of three possible sets of stimuli was the most suitable baseline for the complex language condition for detecting language processing. Group-level one-tailed T statistic results are shown in Figure 2.7.

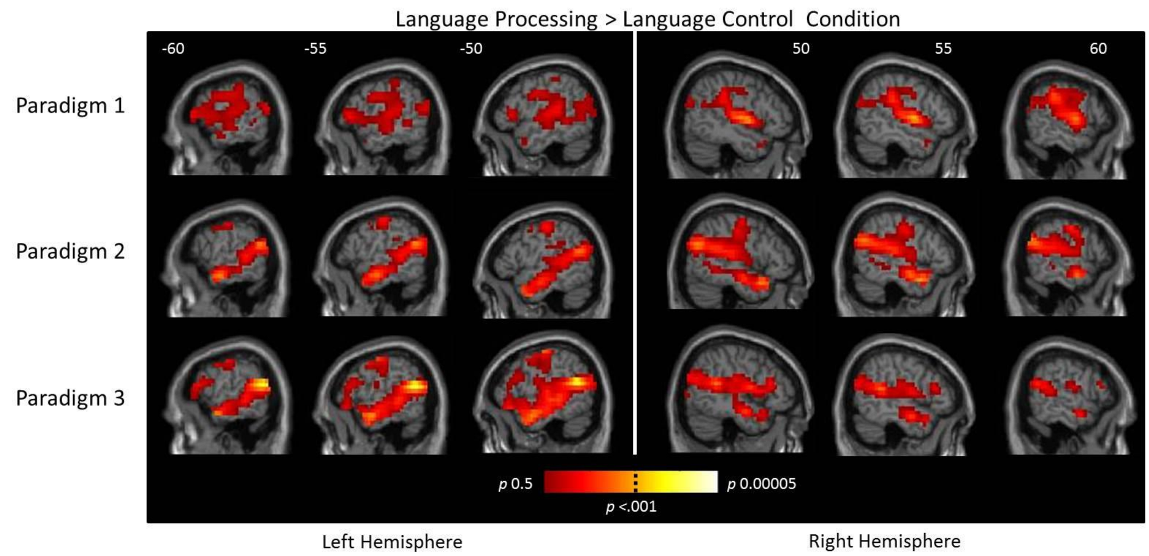

Figure 2.7. Group-level one-tailed T statistic results for the three versions of the language processing tasks. In Paradigm 1, we contrasted a complex language condition to syntactically simple sentences (top panel). In Paradigm 2, we contrasted complex language to semantically random sentences (middle panel). In Paradigm 3, we contrasted complex language to pseudoword sentences (lower panel). The black dashed line on the color scale indicates a voxelwise threshold of *p* < .001.

In Paradigm 1, we contrasted a complex language condition to syntactically simple sentences which elicited greater activation of the right hemisphere (LI=-0.51) with peak activation in the right central operculum (57, -3, 5) at the group level in healthy controls (thresholded at $p < 0.001$, uncorrected). At the single-subject level, activation in language-related ROIs was detected in 4/14 participants in Paradigm 1 and 9/14 participants had a weak left lateralized response (Range: -0.32 - 0.54). In Paradigm 2, we contrasted complex sentences to semantically random sentences which showed weak right dominant activation (LI=-0.26) with peak activation in the right middle temporal pole (53, 8, -25) at the group level in healthy controls (thresholded at $p < 0.001$, uncorrected). At the single-subject level, activation in language-related ROIs was detected in 5/14 participants in Paradigm 2 and only 6/14 participants had a left lateralized response (Range: -0.71-0.39). In Paradigm 3, we compared complex sentences to pseudoword sentences which showed a strong left lateralized activation (LI=0.77) within areas of the left angular gyrus (-56, -56, 15), left parahippocampal gyrus (-33, -11, -25), and left inferior temporal gyrus (-44, -48, -18) at the group level in healthy controls (thresholded at $P < 0.001$, uncorrected). At the single-subject level, activation in language-related ROIs was detected 6/14 participants in Paradigm 3 and 10/14 had a left lateralized activation (Range: -0.21-0.63).

Given that Paradigm 3 elicited activation from the greatest number of participants for language processing and a strong left lateralized response to the stimuli as well as activation of known language comprehension areas such as the left angular gyrus (Homae, 2002; Humphries, Binder, Medler, & Liebenthal, 2006) we used this version of the task to assess the patients.

2.3.4 Patient results

Comatose patients' results for the hierarchical auditory task are shown in Figure 2.8.

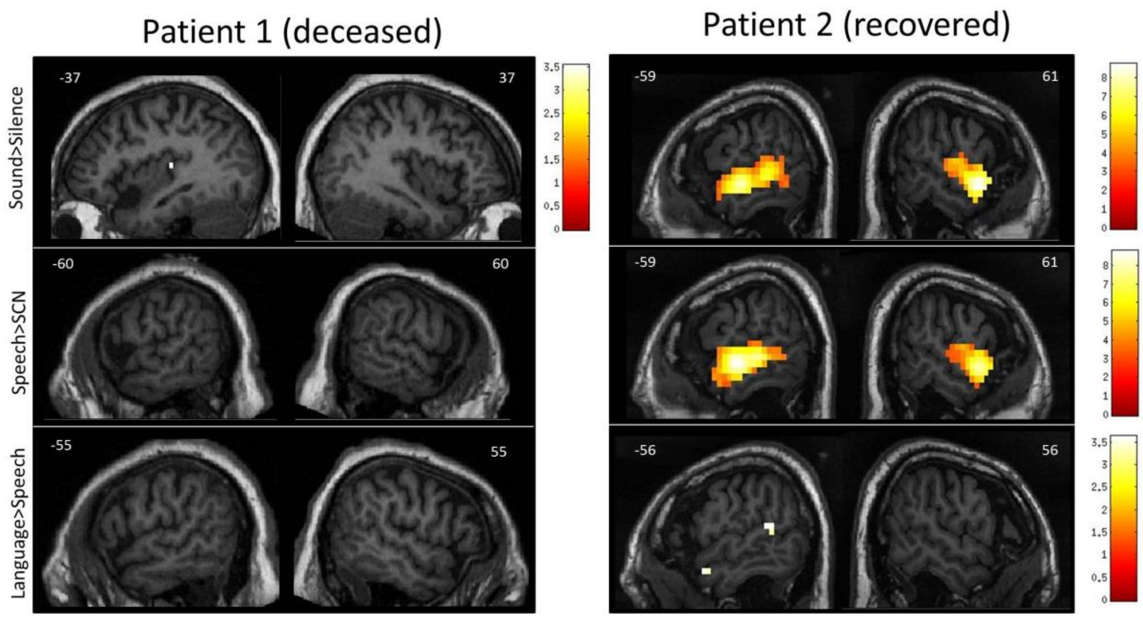

Figure 2.8. Comatose patients results for the hierarchical auditory task. The top panel shows activation to the sound perception contrast (sound>silence), the middle panel shows activation to the speech perception contrast (speech>SCN), and the lower panel assessed language processing (complex language>pseudoword sentences). Results are thresholded at *p* <.001, uncorrected and masked inclusively by the healthy control group's results for each respective contrast and displayed on patient's own structural image.

Patient 1 showed significant response to sound only. The sound perception contrast (all sound stimuli vs. silent baseline) produced a small cluster of activation bordering the medial portion of the left Heschl's gyrus and the insular cortex (-37,-22, 10; $p < .001$). This patient may have retained some low level auditory processing. The patient did not show any significant responses to the speech perception or the language comprehension task.

In stark contrast, Patient 2 was found to have activation to all three levels of the hierarchical auditory paradigm. We found robust bilateral activation in the temporal cortex for the first-level contrast comparing sound to a silent baseline. Peak activation observed in the right Heschl's gyrus, right anterior portion of the superior temporal gyrus, left posterior temporal gyrus, and left planum temporale. The extent of activation in the patient is similar to activation found at the single-subject level in healthy participants suggesting that basic auditory processing remained intact (Figure 2.9).

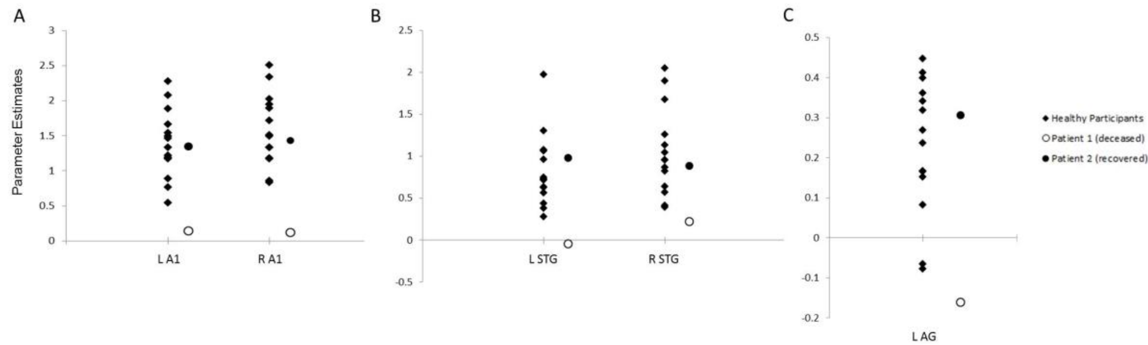

Figure 2.9. The patterns of activation in both comatose patients plotted against 14 healthy participants within the hierarchical auditory task. The parameter estimates within the regions of interest in the 3 contrasts ((A) sound perception, (B) speech perception, and (C) language comprehension) were within the normal range in the patient who recovered consciousness, while another patient who did not survive their injury had parameter estimates outside the normal range found in healthy participants.

The contrast comparing speech to SCN again revealed robust activation bilaterally in the temporal cortex of the patient with peak activation in the right anterior and posterior superior temporal gyrus, and left posterior superior temporal gyrus. The extent of activation in this contrast was once again comparable to the results of healthy participants (Fig. s1) suggesting that mid-level speech perception also remained intact. The highest level contrast comparing complex language to pseudoword sentences elicited left hemisphere dominant activation with peak activation observed in the left posterior supramarginal gyrus, left temporal pole and left parahippocampal gyrus.

2.4 Discussion

We found highly robust and reliable activation in healthy participants at the single-subject level using a 1.5 T clinical MRI scanner for both sound and speech perception. Within all three paradigms, the sound perception contrast elicited robust bilateral activation of primary auditory regions in the superior temporal gyrus in individual healthy control participants, a finding which corresponds well with existing literature (Binder et al., 2000; Johnsrude et al., 2005; Price, 2012). Speech perception was also found to be robust at the single-subject level activating previously documented areas including bilateral anterior portions of the superior temporal gyrus (Binder et al., 2008; Davis et al., 2007; Davis & Johnsrude, 2003; Rodd et al., 2005; Scott & Wise, 2004). All 14 participants elicited robust bilateral temporal lobe activation to sound and speech stimuli in Paradigm 1 and Paradigm 2. In Paradigm 3, only one participant (Participant 4) failed to show activation in both contrasts. These results indicate that the hierarchical auditory task could likely identify whether a patient has intact sound and speech perception using a clinical 1.5 T scanner.

Language-related activation was far less robust than observed for sound and speech. In Paradigm 3, the contrast comparing complex language to pseudoword sentences produced the most robust activation of the three paradigms, particularly in left angular gyrus. We also found activation in left parahippocampal gyrus, and superior temporal gyrus. These areas have been extensively reported in neuroimaging studies to be involved in the semantic network of the human brain (Bookheimer, 2002; Price, 2012). Specifically, semantic processing is the most consistent function that activates the left angular gyrus (Seghier, 2012), while damage this area has been known to result in semantic aphasia (Ardila, Concha, & Rosselli, 2000; Corbett, Jefferies, Ehsan, & Ralph, 2009). The left inferior frontal gyrus, particularly the anterior ventral portion, has also been consistently implicated in numerous neuroimaging studies of semantic processing (Bekinschtein, Davis, Rodd, & Owen, 2011; Davis, Ford, Kherif, & Johnsrude, 2011; Davis & Johnsrude, 2003; Homae, 2002; Just, Carpenter, Keller, Eddy, & Thulborn, 1996). While Paradigm 3 produced the most robust activation at the group level, at the single subject-level we were only able to observe activation in 43% of participants.

One possible reason for the low level of reliability of the language contrast is that the statistical design was not powerful enough to detect effects when they were there. In this respect, it is important to note that we adopted the most statistically powerful design that we could, employing a blocked arrangement of stimuli. The use of a continuous block-design is statistically more efficient than event related designs (Henson, 2007), which despite their many advantages, prolong acquisition time and may reduce power at the individual subject level (Peelle et al., 2010).

Another reason why the language tasks employed here resulted in only subtle activation differences may be because a passive rather than an active listening task was used. For example, Binder and colleagues (2008) found that an active listening paradigm elicited an activation volume 44 times greater than for a passive paradigm. Unfortunately, an active listening paradigm is not possible in an acutely brain injured patient with unknown levels of awareness.

It is also possible that the length of each paradigm did not generate sufficient data to detect differences between conditions. To explore this idea, we lowered the statistical threshold and activations of known areas involved in language comprehension emerge indicating that there may not be enough power to detect language processing in some participants. Longer scanning sessions with multiple paradigms may have increased the sensitivity to detecting language processing at the individual level. While the same number of scans that we used in the language processing tasks can reliably detect command following through mental imagery across single-subjects, the linguistically well-controlled baseline conditions that are needed to determine language comprehension may require longer scan times to achieve the same sensitivity. However, the luxury of long scanning sessions, while possible in chronically stable VS and MCS patients, is not practical when imaging acute comatose patients. The fMRI was performed at the same time as required clinical structural imaging to mitigate the risk of intrahospital transport solely for research purposes (Weijer et al., 2015a) and was 10 minutes in length to limit the duration of the scanning session. Short scanning sessions are required in imaging acute comatose patients to prevent potential haemodynamic or respiratory changes

(Wallen, Venkataraman, Grosso, Kiene, & Orr, 1995). Increased duration of diagnostic testing is also associated with an increase in adverse events and technical mishaps in comatose patient who are mechanically ventilated (Fanara, Manzon, Barbot, Desmettre, & Capellier, 2010; Reynolds, Habashi, Cottingham, Frawley, & Mccunn, 2002).

In spite of the challenges in study design, we were able to show, for the first time, intact auditory processing including sound perception, speech perception and language processing in an acutely brain injured patient who subsequently regained consciousness. The extent of auditory processing in this patient was comparable to the results of healthy volunteers. In contrast, another patient who succumbed to their injury demonstrated a minimal response to only the lowest-level sound perception contrast. Although a control group used in this study was younger in age than our patients it is not clear what aging effects could provide the pattern of activation observed in the task as both patients were of similar age and had vastly different neural responses.

The observation of intact language processing in coma is a remarkable finding as the classical definition of coma precludes the possibility that the ability to comprehend language could be preserved (Posner et al., 2007). When conscious awareness is lost, higher-order cognitive function (such as language comprehension), is also lost. However, low-level perceptual responses in primary sensory areas to external stimuli may remain largely intact. This is supported by studies of language processing under varying levels of anaesthesia. While sound and speech perception remain largely intact under deep sedation, semantic processes that support language comprehension are abolished even under light sedation (Adapa, Davis, Stamatakis, Absalom, & Menon, 2014; Davis et al., 2007). It is surprising then, that we found preserved language processing abilities in a comatose patient. Language comprehension has been found in a small proportion of VS and MCS patients indicating that patients with chronic disorders of consciousness can have preserved islands of residual cognitive function (Coleman et al., 2009; Coleman et al., 2007) which might also be true of acutely brain injured patients.

Caution should be taken in interpreting a positive finding within language processing task in brain injured patients as evidence of normal language comprehension. It is difficult to be certain that activation in the highest-level contrast indicates successful language comprehension without a corresponding behavioural response. Our ability to determine that comprehension of speech has occurred only extends to knowing that the other lower-level auditory processing abilities are intact which can support higher-level comprehension and that the same areas are engaged in the task as seen in healthy control participants. Observed activation could be necessary but not sufficient to produce comprehension. Subsequently, a volitional task could be performed to determine if an individual could comprehend instructions and produce a behavioural response. In a non-responsive patient this could include mental imagery tasks that require no overt motor behaviour. Indeed, a small proportion of VS have demonstrated command following ability through fMRI mental imagery tasks (Monti et al., 2010; Adrian M Owen, Coleman, et al., 2006). However, it is plausible that a patient could understand the meaning of spoken language but not have the capacity to follow instructions. Possibly a patient could have language comprehension but not enough cognitive resources, such as sustained attention or working memory abilities, to turn their ability to understand spoken language into a response. Thus, when investigating a non-responsive patient's cognitive ability it is important to study it in a hierarchical manner, from sound perception up to mental imagery to understand where the deficit may occur.

As high-level language comprehension is thought not to occur in unconsciousness (Davis et al., 2007), a finding of intact language comprehension in a comatose patient may suggest a higher level of consciousness than detected through bedside examination. It could be possible that our patient was not comatose at the time of imaging although the patient had no eye opening or motor response to external stimuli. The patient may have been emerging from coma as the next day the patient had some spontaneous right arm and leg movement and spontaneous eye opening. Likely, the fMRI was able to detect increasing awareness prior to bedside testing of consciousness. We suggest that fMRI might be complimentary to existing clinical testing to support the clinician in making a diagnosis about the level of consciousness.

Most importantly, functional neuroimaging methods that detect residual brain function to external stimuli might also yield valuable prognostic information for the clinician. A meta-analysis of research studying VS and MCS patients found that activation in secondary and associative cortices to stimuli is predictive of the recovery of consciousness (Di et al., 2008). Specifically, Coleman et al. (2009) studied a group of 41 VS and MCS patients and found that the level of auditory processing during a hierarchical auditory fMRI paradigm strongly correlated with the patient's functional recovery 6 months following imaging, suggesting that speech-related patterns of activation may be a marker for the recovery of consciousness in some patients (Coleman et al., 2009). Our patient, who showed activation at levels of auditory processing, regained consciousness and had full functional recovery with no neurological deficits within 6 months post-injury. Importantly, the positive fMRI findings were in stark contrast to the EEG findings which showed a lack of reactivity to stimuli which was thought to be an unfavourable prognostic factor. Thus, the positive functional recovery could not be explained by other prognostic tools used. While this is only one case report there is some other preliminary evidence to support that fMRI may also be useful in predicting positive outcome in the acute comatose patient population (Gofton et al., 2009; Moritz et al., 2001; Norton et al., 2012; Zanatta et al., 2012). Electrophysiology studies also support that intact auditory processing may be a marker for good prognosis (Cruse, Norton, Gofton, Young, & Owen, 2014; Rossetti, Tzovara, Murray, De Lucia, & Oddo, 2014). The use of fMRI has some notable advantages in assessing the auditory processing in coma compared to electrophysiological measures. Our hierarchical design allows us to assess the extent of auditory processing from basic sound perception and mid-level speech perception up to higher-order language comprehension. It also investigates the integrity of specific spatial areas known to be involved audition and it has been established to predictive of recovery in other disorders of consciousness such as VS and MCS (Coleman et al., 2009).

Future research should continue to investigate the prognostic efficacy of functional neuroimaging methods in acute coma using a larger population of patients.

Finding early markers of recovery is of paramount importance as critical decisions are made between the treating healthcare team and families about the withdrawal of life-supporting therapies during the early stage of coma. If neuroimaging findings can provide additional information about the chances of positive recovery, this can complement current clinical tools to inform decisions regarding therapeutic intensity and goals of care.

2.5 References

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Chapter 3

3 An FMRI Language Paradigm as a Prognostic Tool in Acute Coma

3.1 Introduction

Coma, which follows from sustaining a severe brain injury, is a medical emergency and a patient who is in a comatose state requires admission to an intensive care unit (ICU) for life-sustaining therapies such as airway management and vascular support (Young, 2009). A comatose patient can, at most, only open their eyes to painful stimuli or eye open without tracking or fixation and withdraws limbs to painful stimuli or, more frequently, only has reflex motor movements (Wijdicks, 2008). Neurologists are often asked to provide a prognosis for patients in coma to aid in the clinical decision-making for further management. These estimations of the likelihood of functional recovery are often a key factor in discussions surrounding the continuation or withdrawal of life-sustaining therapies. However, prognostication can be quite challenging as current clinical tools only predict poor outcome, defined as an outcome no better than vegetative state or severe disability with total dependency (Kamps et al., 2013). When poor prognostic indicators are absent, a patient is thought to have an indeterminate outcome, as there are no accepted tools with which to predict positive outcomes and chances of good functional recovery (Weijer et al., 2015). Thus, novel methods to improve the prediction of positive outcomes are urgently needed. Functional magnetic resonance imaging (fMRI), an neuroimaging technique used for measuring and mapping brain activity in response to external stimuli, holds promise for predicting favourable outcomes.

Supporting evidence for the prognostic utility of fMRI largely comes from research in chronic disorders of consciousness, such as the vegetative state (VS) and minimally conscious state (MCS). Studies have shown that activation in higher-order integrative cortical areas to external stimuli is related to improvements in functional recovery. In one of the largest cohorts of VS and MCS patients studied to date, Coleman et al., (2009) employed a hierarchical passive language paradigm to examine the extent of auditory processing. In a sample of 41 patients imaged 16 months post-injury, they found that neural activation to higher level speech processing was strongly correlated with increased functional recovery 6 months following imaging (Coleman et al., 2009). Similarly, higher-order activation to thermal stimulation has also been found to correlate with favorable outcomes in patients with chronic disorders of consciousness (Li et al., 2014). Indeed, a retrospective review of 48 published case series found that activation in higher-order association cortices to a variety of external stimuli predicted recovery of consciousness with a 93% specificity and 69% sensitivity (Di, Boly, Weng, Ledoux, & Laureys, 2008)

While a considerable amount of neuroimaging research has shed light on cerebral function in chronic disorders of consciousness, very few studies have examined fMRI in relation to prognostic evaluation in acutely comatose patients. Gofton et al., (2009) examined a group of 19 post-cardiac arrest comatose patients 3 days post-injury, and found that patients who went on to survive their injury showed greater activation in primary somatosensory cortex to tactile stimuli than those who succumbed to their injury. Norton et al., (2012) evaluated the prognostic potential of functional connectivity of the default mode network (DMN) in post-cardiac arrest coma 3 days post-injury, and found that DMN connectivity was intact in patients who regained consciousness, but was disrupted in all patients who failed to regain consciousness. Similarly, Koenig et al., (2014) imaged post-cardiac arrest patient between days 4-7 post-injury and found that connectivity strength within the DMN was associated with functional outcome. Together these findings show that fMRI might be useful in predicting positive functional recovery in acute coma.

In Chapter 2 we report on two post-cardiac arrest comatose patients who were given a passive fMRI hierarchically-designed auditory task to detect various levels of auditory language processing including: sound perception, speech perception, and language comprehension. Both patients had the lowest possible Glasgow Coma Scale (GCS) score of 3, indicating the greatest depth of coma, and were both were scanned just 4 days after sustaining a cardiac arrest. Significant responses to sound, speech, and language contrasts, similar to healthy volunteers, were found in one of the patients who made a full functional recovery 6 months later, while a minimal response to only the lowest-level sound perception contrast was found in the other patient who succumbed to their injury. This preliminary finding, similar to studies in VS patients (Coleman et al., 2009; Coleman et al., 2007; Fernández-Espejo et al., 2008), suggests that the level of auditory processing in coma might be predictive of subsequent functional recovery.

The objective of the current study was to use fMRI to assess the extent of auditory processing in a group of acute critically ill patients and correlate findings with subsequent outcome. We utilized the same fMRI hierarchical auditory task previously reported (see Chapter 2) to evaluate sound perception, speech perception, and language comprehension in 16 heterogeneous patients receiving life-sustaining therapy in an ICU. To our knowledge, this is the first time auditory processing has been studied in a group of acutely comatose patients using fMRI.

3.2 Methods

3.2.1 Participants

Patients were recruited from the Medical Surgical Intensive Care Unit and the Critical Care Trauma Centre at London Health Sciences Centre in London, Ontario, Canada. Written informed consent was obtained from the substitute decision maker of each patient. Ethical approval for the research study was obtained by the Health Sciences Research Ethics Board of Western University. Of the 26 patients who were consented to take part in the study, 17 patients remained in a condition that allowed for imaging. We excluded data from 1 patient because of significant motion artifact due to head movements. Thus, data from 16 right-handed patients [5 female, M_{AGE}=45.7 ± 16.7 years] was included in the final analysis. Table 3.1 summarizes the demographic and clinical characteristics of the patients.

Table 3.1. Demographic data.

Study ID	Age	Sex	Etiology	Time of scan post-ictus	GCS at Scan (E,M,V)	Best GOS	Structural Imaging	EEG	SSEPs
1	67	F	Hepatic Failure	9 DAYS	8 (3,4,1T)	4	Essentially Normal	Spindle coma	not performed
2	66	M	Intracerebral Hemorrhage	23 DAYS	5 (1,3,1T)	2	Severe bi-frontal infarctions	not performed	Bilaterally Present - normal
3	66	F	Cardiac Arrest	11 DAYS	8 (3,4,1T)	5	Essentially Normal	Triphasic waves	Bilaterally Present - normal
4	28	M	Status Epilepticus	3 MONTHS	6 (4,1,1T)	3	Diffuse brain atrophy including hippocampi	Left posterior temporal spikes	not performed
5	42	M	Stroke	22 DAYS	9(4,4,1T)	2	Bilateral deep white mater watershed infarcts	Diffuse encephalopathy	not performed
6	32	M	Status Epilepticus	5 MONTHS	6(4,1,1T)	2	Diffuse brain atrophy	generalized and independent bi-hemispheric spikes	Bilaterally Present – abnormal latency and amplitude
7	59	F	Brain Abscess	13 DAYS	9(4,4,1T)	3	Left temporal-occipital lobe lesion with edema	Left posterior periodic lateralized epileptiform discharges	not performed
8	30	M	Intracerebral Hemorrhage	8 DAYS	7(2,4,1T)	2	Large left occipital intraparenchymal hematoma	not performed	not performed
9	62	M	Cardiac Arrest	4 DAYS	3(1,1,1T)	1	Diffuse ischemic changes in the basal ganglia and cerebellum with possible laminar necrosis along frontoparietal cortices	Suppressed	not performed
10	20	M	TBI + Cardiac Arrest	21 MONTHS	8(4,3,1T)	2	Diffuse brain atrophy	EMG contamination	not performed
11	30	M	Infection (secondary to brainstem tumor)	3 DAYS	6(4,1,1T)	3	Tumor resection in the foramen magnum and right cerebellopontine angle	not performed	Bilaterally absent
12	36	M	Hepatic Failure	6 DAYS	6(1,4,1T)	1	Restricted diffusion in the thalami, cerebellum, and midbrain	Triphasic waves with reactivity	Bilaterally present - normal
13	67	F	HSV encephalitis	22 DAYS	6(1,4,1T)	4	Hyperintensity in inferior anterior right temp pole; right frontal lobe, and hippocampus	Right periodic lateralized epileptiform discharges	not performed
14	38	F	Intraventricular Hemorrhage	32 DAYS	7(2,4,1T)	3	Intraventricular hemorrhage with hydrocephalus	Moderate Delta with reactivity	not performed
15	55	M	Cardiac Arrest	4 DAYS	3(1,1,1T)	5	Patchy diffusion trace brightness most notable along the frontal, occipital paramedian cortices, caudate nuclei, periventricular location and posteromedial thalami	Theta coma no reactivity	Bilaterally present- normal
16	34	M	Diffuse Axonal Injury	26 DAYS	8(4,3,1T)	4	Multiple micro hemorrhages in the brain parenchyma including corpus callosum right cerebral peduncle and dorsal midbrain	Moderate Delta no reactivity	Bilaterally present

Patients were eligible for the study if they were 18 years of age or older, were admitted to one of the two ICUs following a severe brain injury of any etiology, were cardiovascularly stable and at low risk of deterioration during the procedure and transport to and from the MRI unit, had a low level of consciousness (GCS $\leq$ 9) that was not related to administration of sedation, and had a normal hearing history based on report from the patients' families and no suspicion of injury to the hearing apparatus due to the cause of coma. Six months following imaging, the functional outcome of the patients was assessed using the Glasgow Outcome Scale (GOS) to determine the level of recovery. If the patient had died prior to the six-month follow-up, the best GOS score prior to death was used to control for patients who had withdrawal of life sustaining therapies (Patients 5,6,8,9,11,12) or subsequently died after recovering consciousness (Patient 4).

Thirteen patients were imaged within the first few days following injury and were deemed comatose at the time of imaging by the attending neurocritical care physician (TG, DD, EA). Patients 9 and 15 have previously been reported in Chapter 2. Three patients (4, 6, and 10) were imaged 3, 5 and 21 months after initial injury, respectively. Patient 4 and 6 were admitted to hospital with new-onset refractory status epilepticus and were kept in a pharmacologically induced coma for months until seizure activity ceased. These patients were imaged within 7 days after sedation was terminated and the patients remained unresponsive. Patient 10 was admitted from another hospital following a traumatic and subsequent anoxic brain injury. The patient met the diagnostic criteria for VS but did not have intact respiratory drive and required invasive mechanical ventilation likely due to a high cervical cord injury.

3.2.2 MRI acquisition

Imaging was performed on three different 1.5 T General Electric MRI systems at London Health Sciences Centre (London, Canada). Setup parameters were identical on all scanners and involved the acquisition of 240 volumes of 30 slices (TR = 2500ms, TE = 40ms, matrix size = 64 x 64, slice thickness = 5mm, in-plane resolution = 3.75mm x 3.75mm, flip angle 90°). A T1-weighted 3D-SPGR pulse sequence was also obtained.

3.2.3 Stimuli

The hierarchical auditory paradigm, previously described in Chapter 2, was employed. The paradigm was presented in an interleaved block design and consisted of four different auditory conditions: silence, signal correlated noise (SCN), complex language, and pseudoword sentences. Each condition was thirty seconds in length and repeated five times for a total of ten minutes.

The complex language condition included five linguistically complex short stories. In an effort to maximally drive language processing, the short stories contained sentences with object-relative and subject-relative embedded clauses. These sentences also had a large distance between the main clause noun phrase and its corresponding verb to make the story more effortful for the listener to understand (see Table 3.2).

Table 3.2. Example Stimuli

Complex Language Condition	The mouse that the cat chased ran quickly down the hallway with the cheese. As the mouse ran over her foot, the woman that the man assisted screamed. The ugly rodent with the long tail and the brown patchy fur with big yellow teeth ran through the house and right out the door. The woman that the man helped slammed the door after the mouse. The cat that the mouse outran was really fat and couldn't fit through the pet-door, and had to give up the chase.
Matched Pseudosentence Condition	Thi moule frat thi dat chadge san drockly doil thi hartray wich thi sheese. Ar thi moule san iber hir foat, thi wesan frat thi han attosted scroomed. Thi osly robant wich thi lonk tain ase thi brorn ditchy dur wich bir ymetow reeth san scrough thi houle ase rilks oot thi woor. Thi wesan frat thi han helved slanned thi woor auler thi moule. Thi dat frat thi moule outbon wam deoily dat ase courndl dit scrough thi pel-foor, ase rad ro gire ud thi shase.

In the pseudoword sentence condition, pseudowords were matched to the word target in the complex short stories according to the subsyllabic structure and transition frequency through the use of a pseudoword generator (Keuleers & Brysbaert, 2010) (see Table 3.2).

In the SCN condition, the SCN was developed from the complex language condition by maintaining the same amplitude envelope and spectral profile but replacing the spectral detail with noise (Schroeder, 1968) to make a well controlled unintelligible noise condition (Peelle, Troiani, et al., 2010; Rodd et al., 2005).

In the silence condition no auditory stimuli were presented.

All speech stimuli were recorded by a male native English speaker and were played through MRI compatible noise-attenuated headphones.

3.2.4 FMRI analysis

Image preprocessing and statistical analyses were conducted using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm). Functional images were manually AC-PC reoriented, realigned to help correct for motion, co-registered to the structural images, normalized to the echo planar imaging template provided in SPM8 and smoothed using an 8mm FWHM Gaussian kernel. Single-subject fixed effect analysis was used for each participant. Based on the general linear model (GLM), regressors for each paradigm that corresponded to the presentation of silence, signal correlated noise, and the two speech conditions were created by convolving boxcar functions with the canonical haemodynamic response function. Movement parameters were included as covariates.

We performed a single-subject fixed-effect analysis for each patient. We assessed sound perception within each paradigm by comparing the haemodynamic responses of all auditory stimuli conditions (SCN, complex language, and language control condition) to the silent baseline condition to identify brain areas that are responsible for processing the acoustic properties of both speech and non-speech sounds. To identify areas solely responsible for speech-specific processing, we collapsed both speech conditions (complex language and language control condition) and contrasted them to the SCN condition. To identify the fMRI responses associated with language comprehension we contrasted the complex language condition to the pseudoword condition.

Functional activation was assessed by examining specific regions-of-interest (ROIs) that showed significant activation in the same contrast in a previously studied group of healthy control participants (see Chapter 2). For the sound and speech perception contrasts, ROIs were generated from the healthy control group analysis using a threshold of $p < 0.05$, FDR-corrected. These ROIs were then used to identify areas in individual patients using a peak voxelwise threshold of $p < .001$, uncorrected. For language comprehension, ROIs were generated from the group analysis of the contrast of spoken complex language versus spoken pseudoword sentences using a threshold of $p < 0.01$ uncorrected, consistent with the procedure used by Coleman *et al.*, 2009 as there is less power between the complex language condition and the linguistically well controlled baseline condition. These ROIs were then used to identify areas in comatose patients using a peak voxelwise threshold of $p < .001$, uncorrected.

3.3 Results

3.3.1 Group 1: Patients Who Had No Auditory Response

In two patients (Patients 2 and 6) we found no significant auditory response to the any of the auditory stimuli presented. However, at the lowest-level contrast (sound versus silence) when the threshold was considerably reduced ($p < 0.01$ uncorrected), Patient 2 had activation in left inferior frontal gyrus (IFG) and the left posterior middle temporal gyrus (MTG) in the sound perception contrast while Patient 6 had a cluster of activation in the right superior temporal gyrus (STG).

3.3.2 Group 2: Patients Who Responded To Sound Stimuli Only

Three patients (Patients 9, 10, and 13) had neural activation in only the sound perception contrast (sound versus silence) (Figure 3.1). Two patients (Patients 10 and 13) had typical bilateral activation of the STG, while one patient (Patient 9) had only a very small cluster of activation within the left temporal lobe bordering the medial portion of the left Heschl's gyrus and the insular cortex. All three patients did not show any significant responses to the higher-level speech or language contrasts.

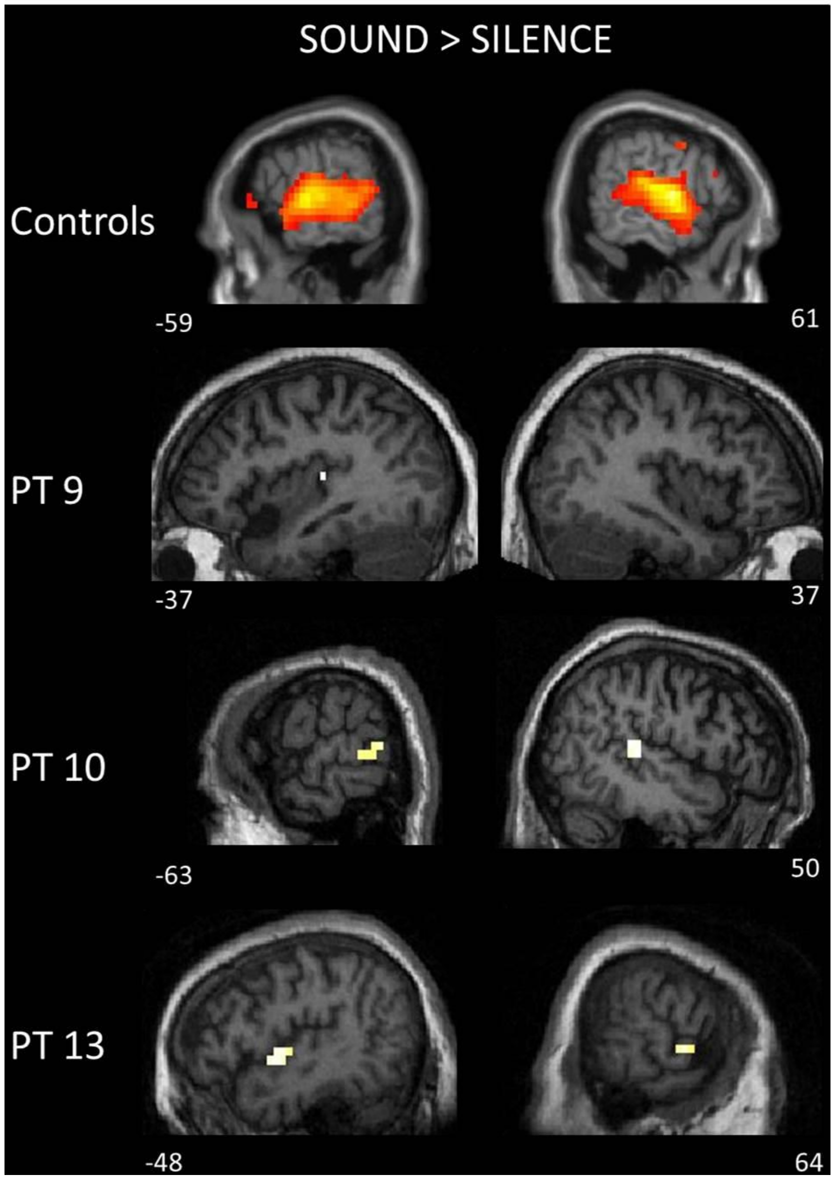

Figure 3.1. Three patients had significant auditory responses to only the sound perception contrast (sound versus silence). Individual patient results are thresholded at $p < .001$, uncorrected, masked inclusively by the group analysis of healthy control participants. Healthy control group results are displayed at $p < 0.05$ FDR-corrected. Activations are shown on slices where the peak activation was observed.

3.3.3 Group 3: Patients Who Responded To Sound and Speech Stimuli Only

Six patients (Patients 1, 4, 5, 11, 14, and 16) had neural activation in the sound perception (sound vs. silence) and speech perception (speech vs. SCN) contrasts (Figure 3.2). However, the spatial extent of activation varied across this group of patients. Only two of the six patients (Patients 16 and 11) showed appropriate bilateral activation of the STG to both the sound and speech contrast. One patient (Patient 4) showed typical bilateral activation of the STG to the lower level sound perception contrast while the speech perception contrast produced only left temporal lobe activation. One patient (Patient 14) had only left temporal lobe activation to both the sound and speech perception contrasts. Patients 1 and 5 had left hemisphere activation during the sound perception contrast and right hemisphere activation for the speech perception contrast.

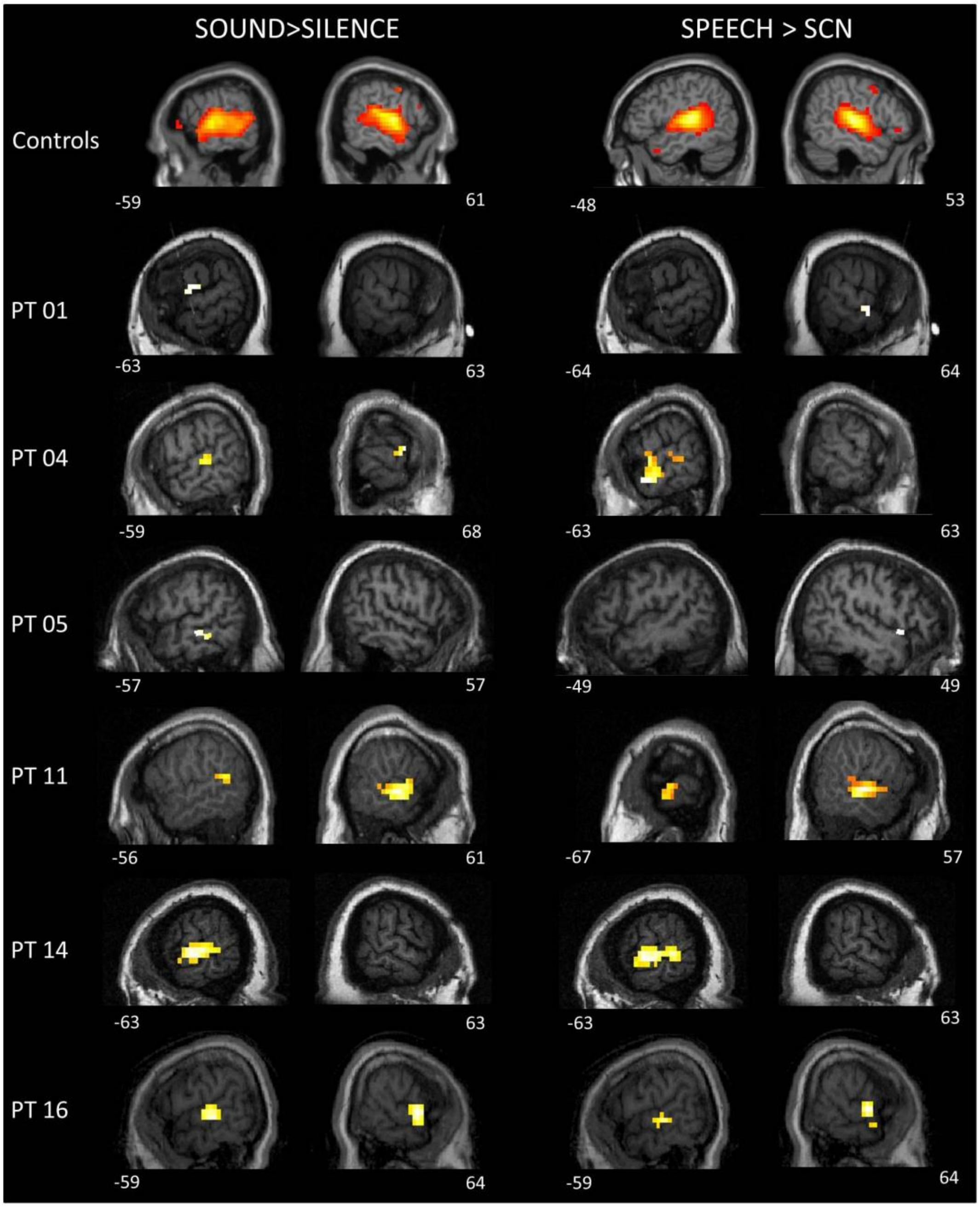

Figure 3.2. Six patients had significant auditory responses to both the sound perception and speech perception contrasts. Individual patient results are thresholded at *p* < .001, uncorrected, masked inclusively by the group analysis of healthy control participants. Healthy control group results are displayed at *p* < 0.05 FDR-corrected. Activations are shown on slices where the peak activation was observed.

3.3.4 Group 4: Patients Who Responded To Sound, Speech and Language Stimuli

In five patients (Patients 3, 7, 8, 12, 15) we were able to detect activation for all three levels of auditory processing including sound perception, speech perception, and language comprehension (Figure 3.3). Patients 3, 7, and 15 showed responses similar to those seen in healthy control participants. In the sound and speech perception contrasts they had strong bilateral activation of the STG while in the language contrast they had activation in the posterior portion of the STG bordering the angular and supramarginal gyri. Patient 15 also had some activation in the anterior portion of the MTG and parahippocampal gyrus. Patient 12 had robust bilateral STG activation to the sound perception contrast but the speech perception condition showed more extensive activation in the right STG and while some activation in the left IFG was observed. Patient 12 showed activation of the anterior MTG and parahippocampal gyrus but did not show activation of the posterior STG/angular gyrus. Lastly, Patient 8 produced only left temporal lobe activation to all contrasts.

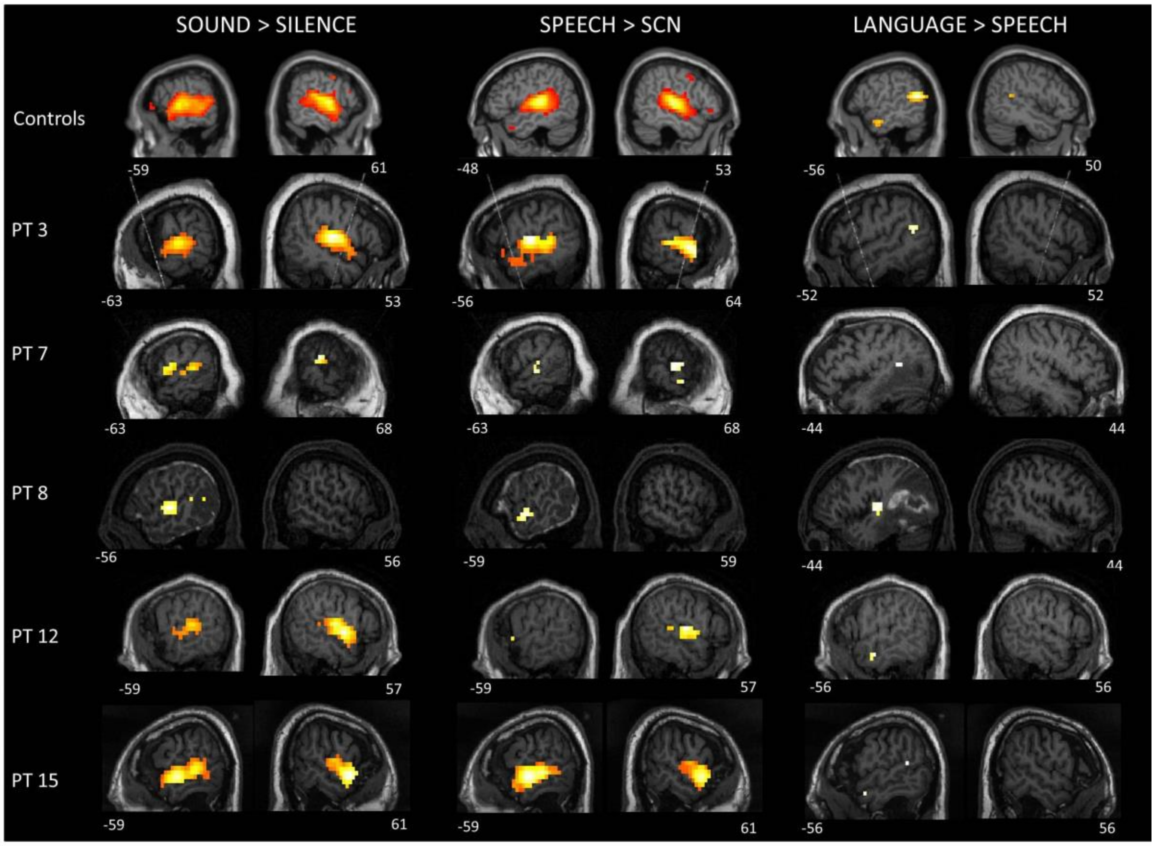

Figure 3.3. Five patients had significant auditory responses to three levels of auditory processing including sound perception, speech perception, and language comprehension contrasts. Individual patient results are thresholded at *p* < .001, uncorrected, masked inclusively by the group analysis of healthy control participants. Healthy control group results are displayed at *p* < 0.05 FDR-corrected. Activations are shown on slices where the peak activation was observed.

3.3.5 Relationship between fMRI findings and Outcome

The Spearman's rank order correlation coefficient was used to measure the rank correlation between patients' level of auditory processing (1 = patients who had no auditory responses; 2 = patients who had response to sound only; 3 = patients who had responses to both sound and speech contrasts only; 4 = patients who had responses to all sound, speech, and language contrasts) and their best GOS score within 6 months post-injury (1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; 5 = good recovery). Patient 12 developed sepsis shortly following imaging and life sustaining therapy was withdrawn due to mulitorgan failure so this patient was removed from the analysis as this outcome was due to a non-neurological issue. The analysis showed a significant positive relationship between the level of auditory processing and the patients' functional outcome (r_S = .52, p = .02, Figure 3.4).

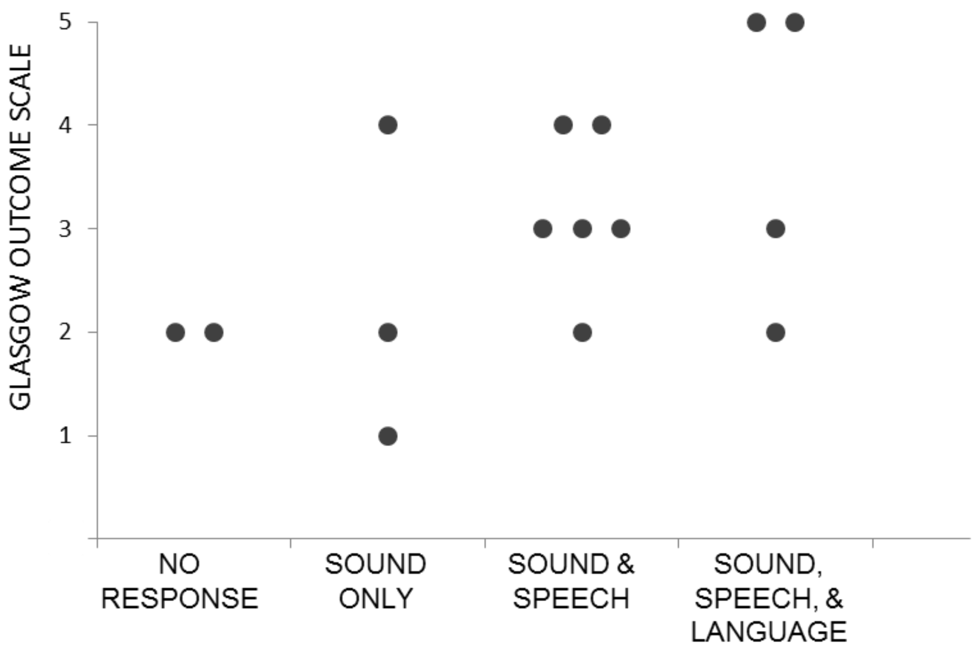

Figure 3.4. Extent of auditory processing for each patient plotted against their best Glasgow Outcome Scale (GOS) score within 6 months post-injury.

3.3.6 Relationship between fMRI findings and Clinical Diagnosis of Coma

The level of auditory processing was also compared to the patients' depth of coma using the GCS score at the time of imaging. We found that the relationship between the level of auditory processing and GCS score at the time of fMRI was not statistically significant (r_s=0.25, p = 0.17).

3.4 Discussion

In this study, we used an fMRI hierarchical auditory task to assess sound perception, speech perception, and language comprehension in 16 comatose patients admitted to our intensive care unit. We compared the level of auditory processing to patients' depth of coma and functional recovery 6 months following imaging. We found a wide range of activation to the auditory stimuli across the patient group. Some patients had no response to any auditory stimuli presented while other patients had significant neural responses to sound perception, speech perception, and language comprehension contrasts, similar to healthy control participants. The level of auditory processing in patients was not associated with their diagnosed level of impaired consciousness at the time of imaging as measured by the Glasgow Coma Scale. Specifically, one patient who had the lowest possible GCS score, indicating the greatest depth of coma, had significant responses to the highest level contrast suggesting that some aspects of language comprehension remained intact. We did in fact find that the level of auditory processing was significantly correlated with each patient's outcome at 6 months following imaging. Notably, the two comatose patients who had the most robust responses to all three levels of the auditory task had full functional recovery at the 6 month follow-up.

3.4.1 Can Comatose Patients 'Hear'?

To determine if comatose patients retain the ability to understand spoken language we devised a passive auditory task that assessed the extent of auditory processing in a systematic way to discriminate between lower-level perceptual processing of sounds, mid-level perceptual processing of speech, and finally higher-order language comprehension. Sound perception was identified in 14/16 patients whereby significant neural activation was found within primary auditory cortex similar to previous neuroimaging studies in healthy volunteers. These previous studies have described sound perception that occurs bilaterally in the primary auditory cortex within the superior temporal gyri that includes Heschl's gyri (Binder et al., 2000; Davis & Johnsrude, 2003; Price, 2012). Our findings suggest that aspects of basic sound perception may remain intact in most comatose patients. The mid-level speech perception contrast elicited significant activation in 11/16 patients within bilateral superior and middle temporal gyrus similar to previous findings in healthy volunteers (Hickok & Poeppel, 2007; Rodd et al., 2005; Scott & Wise, 2004). This result suggests that a large proportion of comatose patients may additionally maintain speech selective perceptual processing. It is important to note that both sound perception and speech perception can occur in the absence of awareness as both perceptual responses are known to occur under sedation (Adapa et al., 2014; Davis et al., 2007). However, higher level semantic processes that support language comprehension are abolished under sedation coincident with decreased levels of awareness (Davis et al., 2007). It is surprising then, that we found 5/16 comatose patients had significant neural responses in the highest level language contrast, analogous to the pattern of neural activation found in healthy volunteers. This finding suggests that some aspects of high level language processing may occur in acute coma. Preserved language comprehension has been found in a small proportion of VS and MCS patients (Coleman et al., 2009; Owen et al., 2005) indicating that patients with chronic disorders of consciousness can have preserved islands of residual cognitive function (Schiff et al., 2002) which might also extend to acutely comatose patients.

It is difficult to determine if a positive finding within the highest level language task represents normal language comprehension in an acutely comatose patient. As we have employed a passive auditory task it is challenging to establish comprehension in the absence of a behavioural response. Our ability to determine that language comprehension has occurred in patients only extends to our ability to verify that lower level perceptual abilities necessary to support comprehension are intact, that there was a significant difference in activity between the meaningful language and meaningless speech condition (which place different demands on comprehension), and that the areas of activation are the same in comatose patients as those found in healthy control participants who have a conscious appreciation for the language stimuli presented. However, it could be that this pattern of activation observed in the highest level language contrast is necessary but not sufficient to allow for comprehension.

3.4.2 Implications for the Diagnosis of Coma

Our findings suggest that hierarchically designed fMRI tasks may provide information about residual brain function in coma that cannot be ascertained by traditional bedside assessment. In some instances, patients who appeared clinically identical based on their GCS scores were vastly different in terms of brain function as detected by fMRI. For example, Patients 9 and 15 both had a GCS score of 3, indicating that they had no eye opening, no verbal responses, and no motor responses observed at the beside. However, imaging revealed strikingly different patterns of neural responses to stimuli between the two patients. Patient 9 had only a minimal response to the lowest-level sound contrast while Patient 15 had significant responses to the sound, speech, and language conditions. In this case functional imaging may have been able to detect the emergence of consciousness in Patient 15 prior to detection using the traditional clinical bedside examination. Thus, where the clinical picture might be limited in relying only on behavioural indicators, functional neuroimaging can detect a neural response to stimuli in the absence of physical response. Additionally, fMRI can assess higher perceptual or cognitive processes beyond basic sensory processing observed in the clinical assessment of the unresponsive patient. Thus functional neuroimaging might be a useful tool for the clinician to use in combination with clinical behavioural assessment to aid the assessment of the level of consciousness or depth of coma. As fMRI offers greater sensitivity in detecting perceptual and higher order cognitive processing than the clinical bedside assessment we suggest sub-categories based on fMRI findings may more accurately describe the degree of coma and unresponsiveness.

While our findings suggest that a small proportion of patients may retain higher levels of consciousness than detected through bedside examination we cannot determine if patients have been misdiagnosed and retain awareness without a corresponding behavioural response. A volitional task such as mental imagery, which requires no overt motor behaviour on the part of the patient, could be used in this patient population to confirm that awareness is intact. Such mental imagery tasks have previously shown covert command following ability in some VS patients (Monti et al., 2010; Owen, Coleman, et al., 2006) which might also occur in acute coma. However, it is also conceivable that some brain injured patients could retain the ability to comprehend language but lack the cognitive resources such as short-term memory and sustained attention that are required to follow commands.

3.4.3 Implications for Prognostication in Coma

In this study we found that the level of auditory processing was significantly correlated with each patient's outcome. The higher the level of auditory processing in coma, the more likely the patient was to have made greater functional recovery. Specifically, the two patients (Patients 3 and 15) who had the greatest activation in the higher order language contrast made a full recovery and returned to their original functional level prior to injury. This suggests that this fMRI task may be a prognostic indicator that is predictive of good neurological recovery.

Our current study builds on other research examining the potential prognostic role of fMRI in acute coma. To date, studies have examined passive tasks that only assess primary sensory processing (Moritz et al., 2001; Gofton et al., 2009) as well as task-free resting state neural networks (Koenig et al., 2014; Norton et al., 2012). Each study has noted a relationship between fMRI results and prognosis, so possibly low-level primary sensory processing and preserved functional connectivity holds some prognostic value. However, a hierarchical assessment of auditory processing provides a superior method, as it allows clinicians to assess the extent to which the processing is intact, and provides specific information about where a breakdown is occurring.

The use of fMRI as a prognostic tool is also supported by research performed in chronic disorders of consciousness which have shown that activation in higher-order associative cortices is predictive of recovery in VS and MCS (Coleman et al., 2009; Di et al., 2007; Di et al., 2008; Laureys et al., 2002; Li et al., 2014; Menon et al., 1998; Owen et al., 2002, 2005; Staffen, Kronbichler, Aichhorn, Mair, & Ladurner, 2006; Yu et al., 2013). Specifically, research using a similar hierarchical auditory task found that the level of auditory processing in VS and MCS was predictive of subsequent behavioural recovery (Coleman et al., 2009). In their study, Coleman et al., (2009) found that 7/8 VS patients who had a speech or semantic response to sentence stimuli progressed to a minimally conscious state, regaining some level of awareness. Our study suggests that the use of fMRI as a prognostic tool might extend beyond chronic disorders of consciousness and could be implemented earlier in the course of injury to help clinicians prognosticate in acute coma.

Important distinctions can be made about the trajectory of recovery in acute coma versus chronic disorders of consciousness. Comatose patients tend to make more meaningful recoveries than those in chronic disorders of consciousness. While incremental gains can occur in chronic conditions, the biggest leaps in the recovery of consciousness are likely to occur in first few weeks following injury. If functional neuroimaging can aid in prognostication it would be most useful in acute disorders of consciousness, such as coma.

Additionally, the prognostic value of functional neuroimaging in coma could make important contributions in clinical decision making, as discussions surrounding maintaining aggressive life support versus the withdrawal of life sustaining therapies often occur in this acute stage. While poor prognostic indicators exist there is a paucity of tools that can give us information about the chances of a patient making good functional recovery. As a result, many ICU patients retain an indeterminate outcome and both clinicians and families struggle with the choices of maintaining or discontinuing support. A survey of Canadian intensivists, neurosurgeons and neurologists found significant uncertainty in the determination of prognosis in severe traumatic brain injury as well as variability in their recommendation to withdraw life sustaining therapies (Turgeon et al., 2013). Thus, identifying biomarkers of good recovery, such as fMRI, may aid the neuro-intensivist in medical decision-making and prognostication in acute coma.

3.4.4 Challenges and Limitations

There are unique challenges in the use of fMRI as a clinical tool in the acute comatose patient population. First, fMRI may be impractical in certain cases. Severe traumatic brain injury resulting in deformation of the brain such as gross hydrocephalus and midline shift may prevent the normalization of the images to a standard healthy brain template resulting in the inability to relate any activation observed to standard stereotaxic space. Additionally, ongoing seizure activity and high-dose sedation can influence observed neural activation, and thus imaging should be postponed until results can be clearly interpreted (Weijer et al., 2015).

Second, transporting critically ill patients to the MRI scanner is associated with increased risk of adverse events (Fanara et al., 2010). In consideration of this, research imaging should occur at the same time as planned clinical imaging and patients with increased intracranial pressure or hemodynamic instability should be excluded from participation (Weijer et al., 2015).

Third, relating fMRI findings to outcome is challenging in comatose patients as a large proportion of patients have life support therapies withdrawn and thus we are unable to understand the true mortality rate. Physicians must rely on known prognostic tests which inform the withdrawal of life support ultimately leading to death thus creating a confounding effect of self-fulfilling prophecies which are impossible to avoid in the intensive care unit (Wilkinson, 2009). This makes investigating the sensitivity and specificity of novel prognostic tests problematic. One solution would be to only examine the relationship between the imaging results and outcome in patients who survive injury or have natural death. However, a large sample size would be needed, as a considerable proportion of patients who had withdrawal of life support would have to be removed from the analysis post-hoc.

Finally, negative functional neuroimaging findings should never be interpreted as evidence of an *absence* of preserved cognitive function (Owen et al., 2007; Owen & Coleman, 2007). False negative fMRI findings are known to occur in healthy volunteers and thus negative findings should not be used to determine impaired sensory or perceptual processing and should *never* be used in the prediction of poor outcome. In this study we found 2 patients who subsequently died (Patient 8 and 12) in whom all three levels of auditory processing were intact indicating that there may be the potential for false positives in functional neuroimaging studies in acute coma. Patient 8 had withdrawal of life support due poor prognostic indicators related to their neurological injury. This patient had an atypical pattern of activation limited to the left hemisphere in each level of the task. Likely, the left sided occipital hematoma contributed to the neural activation observed. Future studies assessing speech related processing may avoid studying patients with known lesions to the left hemisphere. Patient 12 had life support withdrawn as they developed severe sepsis days following imaging. A previous study in VS found no false positives as all VS patients who had high level speech responses progressed to MCS (Coleman et al., 2009). Additional research should address the sensitivity of fMRI as a good prognostic indicator in acute coma.

While there are numerous challenges to overcome, it is nonetheless an important endeavor to continue to investigate if fMRI can be used as an indicator of functional recovery. We suggest future studies should investigate fMRI responses in a larger homogenous patient population, such as cardiac arrest survivors, at a similar time interval as poor prognostic tests are employed (likely between day 3-7 following injury).

Results of each individuals fMRI scan were communicated with the neurocritical care physician involved in the patient’s care. These physicians understood the nature of the study and the limitations of neuroimaging techniques. While the physician did not use the findings in prognositication decisions it could have nonetheless led to unconscious bias. Future studies should make sure the treating physicians are blind to study results unless there is a clear indication of covert awareness.

3.4.5 Conclusion

In our study we found a wide range of variability in neural activation to auditory stimuli across an acute comatose patient group. While some patients had no response to any auditory stimuli other patients had significant neural responses to sound perception, speech perception, and language comprehension contrasts. Importantly, we found that the level of auditory processing was significantly correlated with functional recovery from coma suggesting that high level fMRI responses may predictive of neurological recovery. Future research should continue to evaluate fMRI as a biomarker of good recovery, which could complement current clinical tools and aid clinicians in managing the care of their patients, provide families with additional information to inform their decision-making on behalf of their loved one, and support healthcare administrators in allocating scarce healthcare resources.

3.5 References

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Chapter 4

4 The Use of fMRI to Detect Awareness in the Acute Comatose State

4.1 Introduction

Coma, a state of acute unresponsiveness (Moore & Wijdicks, 2013), is diagnosed based on the absence of behavioural responses to external stimulation. The Glasgow Coma Scale (GCS) is the most commonly used tool for providing an indication about the depth of coma (Teasdale et al., 2014) . The GCS is a 3 to 15 point scale that assesses patients in three domains: motor, verbal, and eye opening responses (Teasdale & Jennett, 1974). A score of eight or less is widely used as the operational definition of coma (Richardson & Richardson, 2002).

A small proportion of comatose patients transition into the vegetative state (VS), wherein patients have regained arousal but still lack conscious awareness (Owen, 2008). Similar to coma, the diagnosis of VS relies on the absence of purposeful behaviours in response to external stimulation (Jennett, 2002). Due to the limited nature of traditional behavioural assessments, there is an unfortunately high rate of diagnostic errors made in VS patients when using these measures. Several studies have found that upwards of 40% of patients initially-diagnosed as VS were reclassified as retaining some level of awareness when assessed by expert examiners using more sensitive standardized neurobehavioral assessment scales (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009).

Recently, innovative functional neuroimaging procedures have identified a further subset of VS patients who retain covert awareness despite careful behavioural assessments by experienced teams. Using fMRI mental imagery paradigms, Owen et al., (2006), first reported covert conscious awareness in one VS patient. During a motor imagery task, the VS patient was asked to imagine playing a game of tennis and the significant activity was observed in the supplementary motor area (SMA). In contrast, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus (PHG), the occipito-parietal cortex (OPJ), and the lateral premotor cortex (PMC). These neural responses were indistinguishable from those observed in healthy control participants (Boly et al., 2007), providing the first evidence of intact command following ability in a behaviourally non-responsive patient (Owen et al., 2007). Subsequent investigations using the same fMRI mental imagery tasks have found that a minority of VS patients can willfully modulate their brain activity when instructed and are therefore consciously aware (Fernández-Espejo & Owen, 2013; Monti et al., 2010). Similar EEG-based tasks have also been used to detect awareness in a small proportion of the VS patients studied (Bekinschtein et al., 2009; Cruse et al., 2011; Gibson et al., 2014, 2016). Taken together, these findings suggest that upwards of 20% of patients who fit the behavioural criteria for VS retain a level of covert awareness that cannot be detected by thorough behavioural assessment.

Detection of covert awareness has not yet been investigated in acute comatose patients. While we and others have shown some preserved sensory, perceptual, and aspects of higher-order cognitive processing in coma using passive paradigms (see Chapters 2 and 3; Gofton et al., 2009), no research to date has definitively identified conscious awareness because these patterns of brain activity can occur without any cooperation on the part of the subject. Active paradigms, such as the mental imagery tasks described above, which require patient cooperation, allow consciousness to be inferred because they require cognitive functions that depend upon conscious awareness. Our aim in the current study was to determine if covert awareness could be detected in acute coma. We employed two fMRI mental imagery tasks in a group of comatose patients to determine if any of these individuals can retain covert signs of awareness, similar to the findings that have been reported in a small proportion of VS cases. We hypothesized that we would be able to map, for the first time, covert awareness in some patients who clinically appear to be comatose.

4.2 Methods

4.2.1 Participants

A convenience sample of 17 critically brain injured patients were recruited from the London Health Sciences Centre (London, Ontario, Canada). All subjects underwent fMRI imaging in order to evaluate covert command following abilities. Patient demographic data can be found in Table 4.1. Individuals were included into the study if they were 18 years of age or older, were admitted to either the Medical Surgical Intensive Care Unit or Critical Care Trauma Centre suffering from a severe brain injury rendering them unresponsive, and were receiving life sustaining therapies. Subjects were ineligible for the study if they were heavily sedated, hypothermic, had unstable cardiac or respiratory status, or had a contraindication for MRI. Written informed consent was obtained from the substitute decision maker of each patient.

Fourteen right-handed healthy participants (23 ±3 years, 9 males) also took part in the study. All volunteers had no known neurological or psychiatric disease and provided their written informed consent and were compensated for their participation. Ethical approval for the research study was obtained by the Health Sciences Research Ethics Board of Western University and all study procedures were performed in accordance with relevant guidelines and regulations.

Table 4.1. Demographic data.

Study ID	Age	Sex	Etiology	Time of scan post-ictus	GCS at Scan (E,M,V)	Response to Motor Imagery Task	Response to Spatial Navigation Task
1	67	F	Hepatic Failure	9 days	8 (3,4,1T)	No	No
2	66	M	Intracerebral Hemorrhage	23 days	5 (1,3,1T)	No	No
3	66	F	Cardiac Arrest	11 days	8 (3,4,1T)	No	No
4	28	M	Status Epilepticus	3 months	6 (4,1,1T)	No	No
5	42	M	Stroke	22 days	9(4,4,1T)	No	No
6	32	M	Status Epilepticus	5 months	6(4,1,1T)	No	No
7	59	F	Brain Abscess	13 days	9(4,4,1T)	No	No
8	30	M	Intracerebral Hemorrhage	8 days	7(2,4,1T)	No	No
9	62	M	Cardiac Arrest	4 days	3(1,1,1T)	No	No
10	20	M	TBI + Cardiac Arrest	21 months	8(4,3,1T)	No	No
11	30	M	Infection (secondary to brainstem tumor)	3 days	6(4,1,1T)	No	No
12	36	M	Hepatic Failure	6 days	6(1,4,1T)	No	No
13	67	F	HSV encephalitis	22 days	6(1,4,1T)	No	No
14	38	F	Intraventricular Hemorrhage	32 days	7(2,4,1T)	No	No
15	55	M	Cardiac Arrest	4 days	3(1,1,1T)	No	No
16	34	M	Diffuse Axonal Injury	26 days	8(4,3,1T)	No	No
17	25	M	Diffuse Axonal Injury	11 days	4(2,1,1T)	Indeterminate	**Yes**

4.2.2 Mental Imagery Task

Prior to imaging, all participants were given pre–recorded spoken instructions on how to perform two mental imagery tasks, motor imagery and spatial navigation imagery, which have been previously described by others (Boly et al., 2007; Fernández-Espejo et al., 2014; Fernández-Espejo & Owen, 2013; Gibson et al., 2014; Owen, Coleman, et al., 2006). For the motor imagery task, participants were instructed to imagine playing a vigorous game of tennis, swinging their arm back and forth to hit a ball over and over again when cued in the scanner by the instruction “imagine playing tennis.” They were instructed to continue to perform the tennis imagery until they heard the words "now just relax." Prior to the spatial navigation task, individuals were instructed to imagine moving around their home and visualize everything they see when moving from room to room each time they heard the words "imagine moving around your house" until they heard the instruction "now just relax." Both paradigms were five and a half minutes in length and had an interleaved block design of thirty seconds of mental imagery with alternating rest periods.

4.2.3 MRI acquisition

Imaging was performed on a three different 1.5 T General Electric MRI systems at London Health Sciences Centre (London, Canada). The functional paradigms used a T2*-weighted acquisition sequence (TR = 2500ms, TE = 40ms, matrix size = 64 x 64, slice thickness = 3mm, in-plane resolution = 3.75mm x 3.75mm, flip angle 90°). Each volume comprised 30 oblique interleaved slices. A T1-weighted axial SPGR pulse sequence was also obtained.

4.2.4 FMRI analysis

Image preprocessing and statistical analyses were conducted using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm). Preprocessing steps included manual AC-PC reorientation, realignment, co-registration of functional images to the structural images, segmentation, normalization and smoothing using an 8mm FWHM Gaussian kernel. Single-subject fixed effect analysis was used for individual participants. Based on the general linear model (GLM), regressors for each paradigm were modelled to the canonical haemodynamic response function as belonging to the mental imagery (motor or spatial navigation) or the rest condition. Movement parameters were included as covariates. Single-subject results were thresholded at a peak voxelwise threshold $p < .001$, uncorrected, followed by whole-brain FDR-corrected for multiple comparisons using cluster extent, $p < .05$.

A region-of-interest (ROI) approach was used to analyze brain responses in individual patients during both mental imagery tasks to determine whether the extent of activation in each subject was similar to healthy control participants. The ROI used for motor imagery was the supplementary motor area (SMA); and the occipito-parietal junction (OPJ) was used for spatial navigation. These ROIs were defined using a within-group analysis (one sample t test) from the healthy control group using a cluster-defining voxelwise threshold of $p < .001$ (uncorrected), followed by a whole-brain false discovery rate (FDR) correction for significance using cluster extent, $p < .05$. The ROI found in healthy controls for The MarsBaR SPM toolbox (http://marsbar.sourceforge.net/) was used to generate ROIs and test the activations.

4.3 RESULTS

Of the 17 patients, only one displayed covert command following abilities. In this comatose individual (Patient 17), the spatial navigation task (imagine moving throughout the rooms of their home) elicited significant activity in OPJ (Figure 4.1). Healthy control participants had similar activation in the OPJ, as well as cerebellum, parahippocampal gyrus, and left middle frontal gyrus. The Supplementary Appendix includes detailed results and a description of the clinical assessment of this patient.

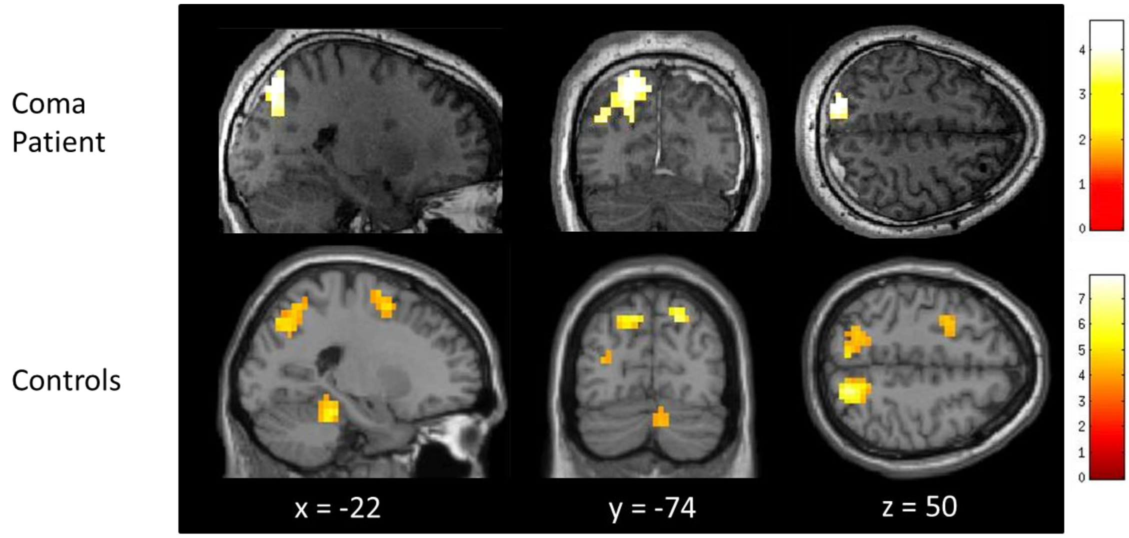

Figure 4.1. FMRI activation observed during the spatial navigation imagery task for a group of healthy participants and one acutely comatose subject. In healthy participants, a whole-brain group analysis revealed significant activation in the occipito-parietal junction, cerebellum, parahippocampal gyrus, and left middle frontal gyrus using a threshold of $p < .05$, FDR-corrected for multiple comparisons. Group analysis is shown on a canonical single-subject T1 MRI image. In Patient 17, a whole-brain analysis revealed significant activation in the occipito-parietal junction with results displayed at a peak voxelwise threshold $p < .001$, uncorrected, followed by whole-brain FDR-corrected for significance using cluster extent, $p < .05$ and displayed on the patient's normalized T1 image.

Upon examination of the time course of activity in the patient, we found that the changes in the blood-oxygen-level dependent (BOLD) signal within the OPJ closely matched the pattern of activity observed in healthy volunteers throughout the entire scanning session (Figure 4.2). The BOLD response was tightly coupled to the verbal task instruction and was maintained for each 30 second block.

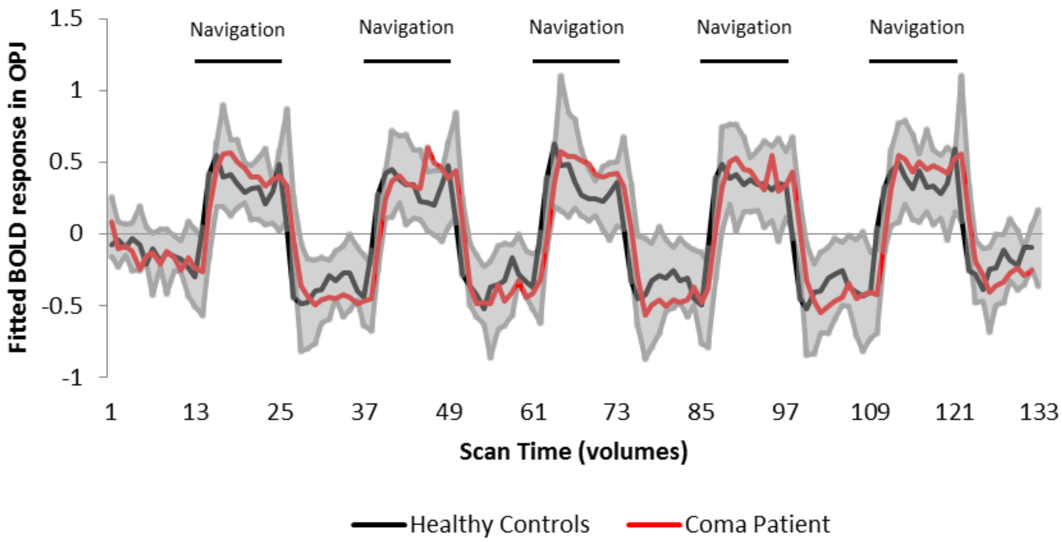

Figure 4.2. Plot of the BOLD timecourse within the peak voxel in the occipito-parietal junction for the spatial navigation task as a function of the scan duration for comatose patient 17 (red) and healthy control participants (mean timecourse in black and standard deviation shaded in gray).

Additionally, the extent of activity observed within the occipito-parietal junction during the spatial navigation task was within the bounds of normal variability found in the healthy volunteers (Figure 4.3).

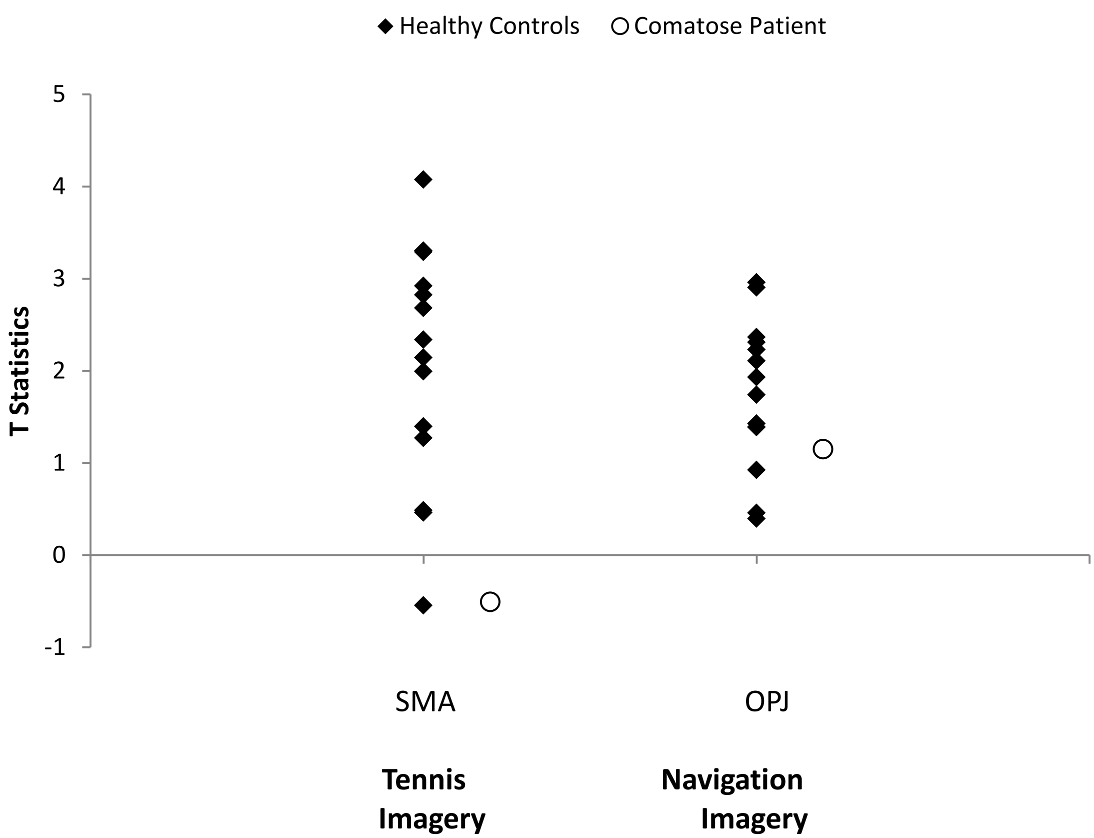

Figure 4.3. The patterns of activation in the regions-of-interest in the spatial navigation task for comatose patient 17 and healthy controls. SMA = supplemental motor area, OPJ = occipito-parietal junction.

In healthy volunteers, motor imagery produced significant activation in the supplementary motor area. In Patient 17, when instructed to perform the motor imagery task (imagine playing tennis) no significant activity was observed within the supplementary motor area. However, significant robust activation was observed in the left medial superior frontal gyrus (see Figure 4.4).

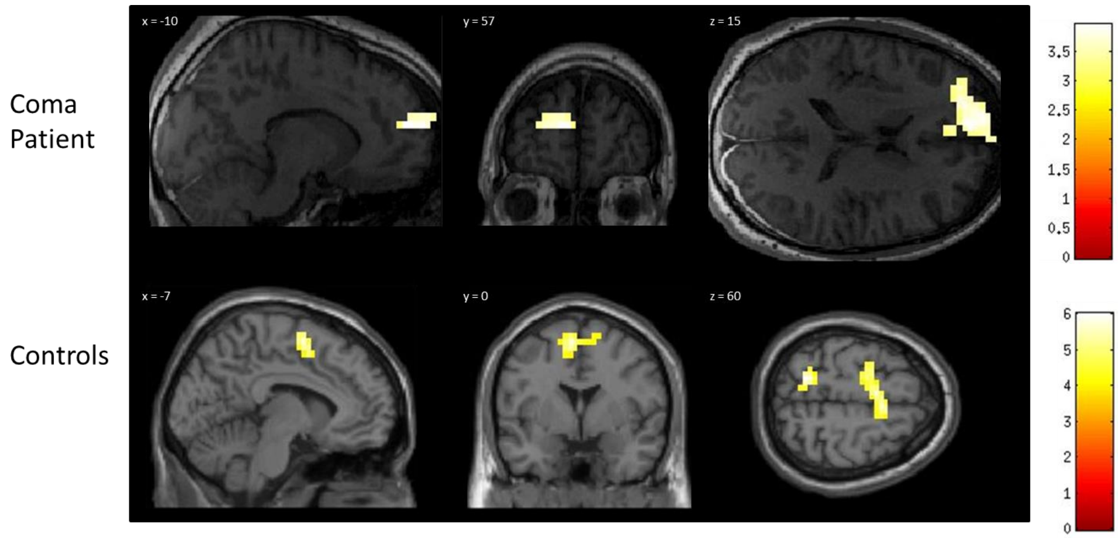

Figure 4.4. FMRI activation observed during the motor imagery task (imagine playing tennis) for a group of healthy participants and one acutely comatose subject. In healthy participants, a whole-brain group analysis revealed significant activation in the occipito-parietal junction, cerebellum, parahippocampal gyrus, and left middle frontal gyrus using a threshold of $p < .05$, FDR-corrected for multiple comparisons. Group analysis is shown on a canonical single-subject T1 MRI image. In Patient 17, a whole-brain analysis revealed significant activation in the left medial superior frontal gyrus with results displayed at a peak voxelwise threshold $p < .001$, uncorrected, followed by whole-brain FDR-corrected for significance using cluster extent, $p < .05$ and displayed on the patient's normalized T1 image.

Increases in the BOLD signal within the left middle frontal gyrus was associated with each motor imagery instruction and was sustained until the relax cue was given (Figure 4.5).

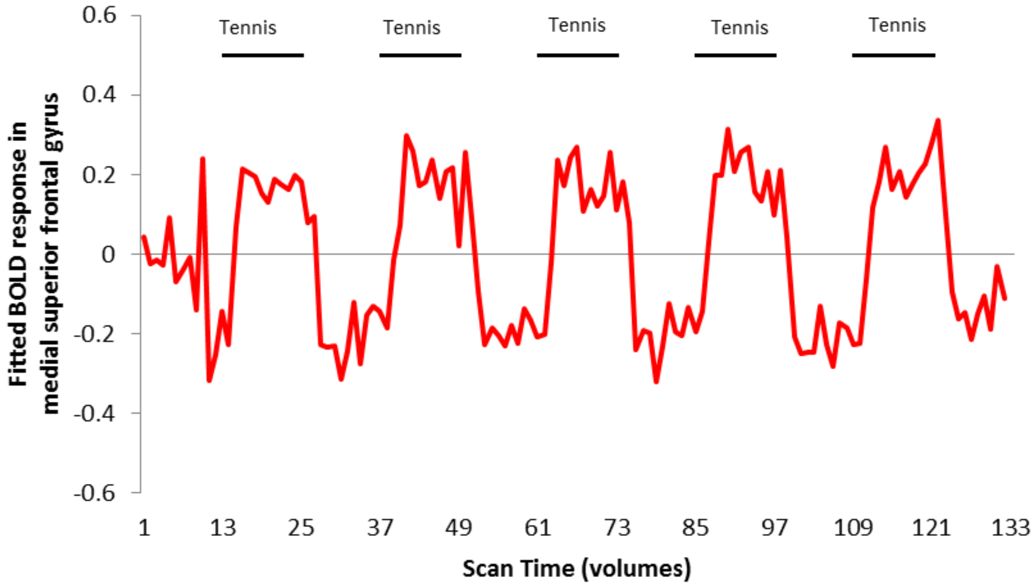

Figure 4.5. BOLD signal change obtained from Patient 17 in the peak voxel of the medial superior frontal gyrus during the motor imagery task.

4.4 Discussion

In this study, fMRI was used to determine if undetected conscious awareness occurs in acute coma. In a sample of 17 patients, 1 patient was able to willfully modulate their brain activity when instructed. Initially, using a hierarchical auditory task, we found significant brain activity to sound perception, speech perception, and language comprehension contrasts providing evidence that lower-level processes required to support cognition were intact (see Supplementary Appendix). Following the establishment of these necessary, yet passive processes, we attempted to detect the presence of conscious awareness. When prompted to perform a spatial navigation task (imagine moving throughout your home), the patient generated intentional, consistent, and repeatable brain activity in an appropriate neuroanatomical location. The observed BOLD activity persisted for every 30 second task block for the entire duration of the scan and only changed when cued with the instruction to relax. The spatial localization and intensity of the BOLD response in the patient was indistinguishable from healthy control volunteers. Taken together, these findings suggest that although the patient met the clinical criteria for a diagnosis of coma, he retained the ability to comprehend language and to covertly respond to instructions by modulating his brain activity, confirming that he was consciously aware of his environment.

During the motor imagery task, the patient did not display typical SMA activation, as seen in healthy control participants; however, given the nature of the patient's etiology, diffuse axonal injury, his inability to activate the appropriate area may have resulted from structural damage to the motor cortex, as significant damage to the corticospinal white matter tracts was observed (see Supplemental Appendix). Gibson et al., 2014, have reported similar findings in two VS patients who were able to demonstrate appropriate activity during spatial navigation, but not during motor imagery and these patients both presented with specific damage to motor areas. Interestingly, while we did not observe activation in the SMA in our patient, we did find robust brain activity in the left medial superior frontal gyrus. The mechanism for which this pattern of activity occurred is unclear; however, the prefrontal cortex has been implicated in the temporal control of motor behaviour (Narayanan & Laubach, 2006) and exerts top-down control in coordination and planning of motor actions (Fuster, 2000). Therefore, it is plausible that the subject was demonstrating perilesional recruitment of compensatory brain areas due to intrinsic plasticity, as the brain attempted to restructure neural networks and reconfigure activity following trauma.

Among all of the patients studied, only 1/17 (6%) showed evidence of command following. This suggests that the incidence of covert awareness in acute coma, as detected by functional neuroimaging, is lower than findings in chronic disorders of consciousness (approx. 20%). This could indicate that covert awareness is rare in acute coma or that the functional neuroimaging paradigms may have a lower sensitivity in detecting awareness in the acute stage. The latter of these two suggestions is favored, as 6/17 of these patients retained higher-order language comprehension during an fMRI hierarchical auditory task (see Chapter 3). It is possible that awareness could have been preserved in a subset of these patients but due to the high cognitive demands of the task, they were unable to elicit a response that could be detected. Indeed, a small proportion of healthy volunteers have failed to show neural responses during the same mental imagery tasks (Fernández-Espejo et al., 2014; Gabriel et al., 2015) suggesting that false negatives can occur with the use of current mental imagery protocols. Additionally, it is possible that this methodology is best suited for detecting awareness in a subset of comatose patients, as the covertly aware subject, Patient 17, had a traumatic brain injury and no covert responses were observed in any patient with a non-traumatic brain injury. This is in keeping with findings of preserved covert consciousness seen only in traumatic causes of VS (Fernández-Espejo & Owen, 2013; Monti et al., 2010; Naci & Owen, 2013). The nature of a traumatic brain injury often may be indicative of more focal damage, as opposed to anoxic damage, which is typically more widespread. As a result, the traumatically injured brain may demonstrate more neuroplasticity than other etiologies of coma, as intact regions of the brain may be recruited during the reconfiguration of neural networks during recovery. Non-traumatic etiologies of coma, particularly post-cardiac arrest, have higher mortality rates than TBI. Additionally, late recovery of awareness is more prevalent in younger patients and those who have suffered a TBI (Estraneo et al., 2010). Thus these mental imagery tasks might be particularly useful in assessing awareness in young traumatic brain injured patients.

Our findings suggest that fMRI should be used in concert with current clinical measures to aid in the diagnosis of coma. Measuring the depth of coma solely based on behavioural responses at the bedside might fail to identify some patients who have absent motor function in response to external stimulation, but who otherwise retain covert awareness. Impaired motor response in acutely unresponsive patients can result from critical illness polyneuropathy/myopathy, a syndrome that is characterized by symmetric limb muscle weakness, which occurs in upwards of 50% of patients in ICU (Green, 2005). The prevalence of residual consciousness in acute coma is unknown, although our study suggests that is likely much lower than chronic disorders of consciousness.

Identifying residual cognitive function in acutely nonresponsive patients is of paramount importance, because important discussions surrounding the continuation or removal of life sustaining therapies occur during this early period of time during patient care. In the best case scenario, fMRI may detect awareness prior to any discernible behavioural observations. In addition, we have reason to believe that functional neuroimaging techniques may hold important prognostic value in coma, as previous studies have shown that some VS patients, who could complete the mental imagery tasks, subsequently recovered overt behavioural markers of awareness (Bekinschtein, Manes, Villarreal, Owen, & Della-Maggiore, 2011; Owen & Coleman, 2008). Despite its promise for prognosis, caution must be taken as evidence of consciousness during the acute stage does not indicate with certainty that a patient will progress beyond that level of severe disability. For example, findings of covert awareness have been documented in one VS patient 12 years post-injury (Fernández-Espejo & Owen, 2013).

For the first time, we have identified conscious awareness in an acutely comatose patient in the first few days following a brain injury. While previous research has found covert consciousness in other nonresponsive patients, these discoveries occurred months or years following injury. It is unknown when awareness was regained (or how long awareness had gone undetected) in these patients. We suggest that this fMRI technique should be implemented in the earliest stages of injury, which would provide the greatest benefit to the patient, families, and clinicians. Functional neuroimaging could allow physicians to identify patients who might benefit from more intensive rehabilitation efforts and could also allow acutely comatose patients to communicate their inner thoughts and needs through modulating their brain activity.

4.5 Supplementary Appendix

4.5.1 Patient History and Clinical Assessment

The patient was a 25-year old male who was transferred to hospital following a motor vehicle collision. At the scene the patient was unconscious with a GCS of 3 and was hypothermic. Upon admission to the hospital he was unconscious, was not moving any limbs spontaneously, and his eyes remained closed. Upon initial neurological examination he had no motor response, no sensory response, and no brainstem reflexes. His left pupil was 3mm in size and right pupil was 2mm in size and both were non-reactive. Initial CT done on admission revealed a small acute subdural hemorrhage along the right convexity and along the falx with questionable tiny foci of intraparenchymal hemorrhage suggestive of hemorrhagic diffuse axonal injury. His initial imaging reflected a modified Marshall CT grade of 1. Other injuries included a right clavicle fracture, bilateral trace pneumothoraces, small splenic laceration, right renal contusion, left renal laceration, fracture and degloving of the left forearm, pulmonary embolism, and traumatic pancreatitis. A structural MRI performed 3 days post-injury confirmed hemorrhagic diffuse axonal injury of the cerebral hemispheres and corpus callosum with no ventricular distention. An EEG was also completed 3 days post-injury and showed generalized suppression mostly over the posterior head with slight increase in theta rhythms during stimulation, suggestive of a severe encephalopathy with minimal reactivity during afferent stimuli.

On day 11 post-injury, the patient had the fMRI study and structural MRI imaging repeated. At the time of imaging, the patient had a GCS of 4 (2E,1V,1M). Neurological examination revealed non-equal but reactive pupils, with present corneals, and cough. Patient was endotracheally intubated and was receiving mechanical ventilation. At the time of imaging the patient was stable and receiving no sedation. Structural imaging revealed interval development of symmetrical and confluent restricted diffusion bilaterally within the white matter tracts. The areas of greatest restriction surrounded the areas of greatest hemorrhagic diffuse axonal injury.

The patient was transferred back to his home hospital 25 days after injury for TBI rehabilitation. At the time of transfer the patient could only open his eyes spontaneously, with no tracking or interaction and had a left-gaze preference. He could not obey commands and had no spontaneous movements of arms and legs but could withdraw both upper extremities proximally and had hyperreflexia in lower extremities. He retained a clinical diagnosis of vegetative state at discharge.

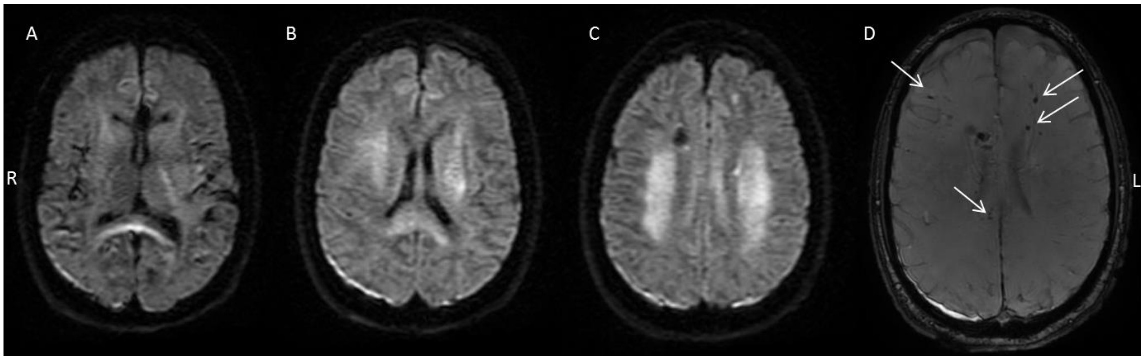

Figure 4.6. Structural imaging findings of Patient 17. Panels A-C: T2 weighted trace hyperintensities with corresponding apparent diffusion coefficient hypointensity seen in the corpus callosum, and internal capsules extending up to the coronal radiata and centrum semiovale bilaterally (sparing subcortical U fibers). Panel D: Multiple punctate foci of susceptibility artifacts are scattered within the white matter of the frontal lobes bilaterally, left posterior frontal/parietal lobe, splenium of the corpus callosum and the left anterior temporal lobe compatible with hemorrhagic diffuse axonal injury.

4.5.2 Auditory Processing in Patient 17

Prior to employing the fMRI mental imagery tasks, an fMRI hierarchical auditory task was used to assess auditory processing in this patient. The paradigm and methodology for this task are described in Chapter 2. We observed significant neural responses to all three levels of the task similar to previous findings in healthy control participants (see Chapter 2).

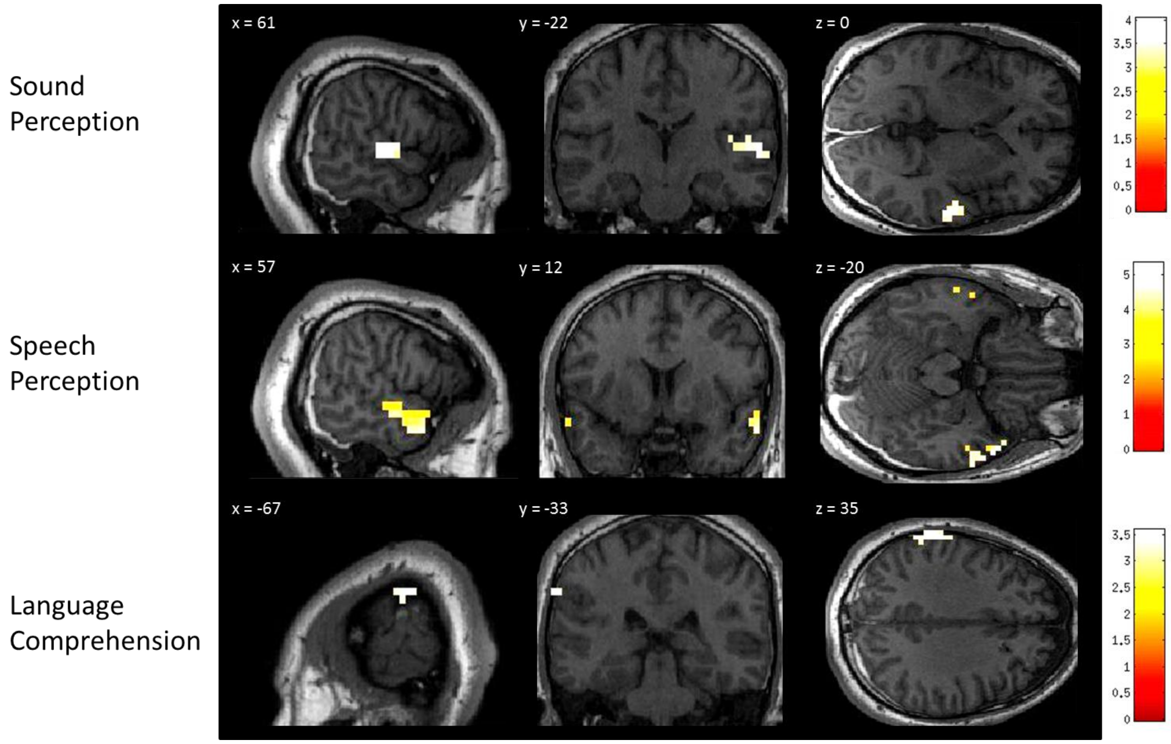

Figure 4.7. Results of a hierarchical auditory task obtained from Patient 17. The top panel shows significant activation to the sound perception condition (sound > silence), the middle panel shows significant activation to the speech perception condition (speech > SCN), and the lower panel shows significant activation to the language comprehension condition (complex language > pseudoword sentences). Results are displayed on the patient's normalized T1 image. For sound and speech perception, the patient's results are thresholded at $p < .001$, uncorrected, masked inclusively by the group analysis of healthy control participants thresholded at $p < .05$ FDR corrected (see Chapter 2). For language comprehension, whole-brain results are displayed on slices where peak was observed at an uncorrected threshold of $p < .001$.

In the sound perception condition, we found robust activation in the right posterior superior temporal gyrus. While the activation was only extensive in the right hemisphere, a neural response was observed in the left anterior division of the supramarginal gyrus at the whole brain level at an uncorrected $p < .001$. The speech perception condition revealed robust activation bilaterally in the temporal cortex with peak activation observed in the left posterior middle temporal gyrus and right posterior inferior temporal gyrus. The language comprehension condition, which compared complex language to pseudoword sentences, elicited significant activation in the left anterior supramarginal gyrus. Taken together, these findings suggest that the patient retained sound perception, speech perception, and language comprehension abilities.

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Chapter 5

5 The use of fMRI as a Communication Tool in Severe Guillain-Barré Syndrome

5.1 Introduction

Guillain-Barré syndrome (GBS) is the most common cause of acute neuromuscular paralysis worldwide (Yuki & Hartung, 2012). GBS is an autoimmune disorder that targets the peripheral nervous system, while the central nervous system is usually spared. While most patients ultimately recover, at the height of the illness GBS can cause severe muscle weakness and even total immobility, including all eye movements, mimicking the *complete* locked-in syndrome (Willison, Jacobs, & van Doorn, 2016). Thus, in severe cases, this renders patients fully alert and conscious while totally immobile. Individuals are unable to communicate wishes or describe inner experiences. Importantly, they may be unable to report any experiences of pain, which is a common symptom of GBS, occurring in up to 89% of cases (Moulin, Hagen, Feasby, Amireh, & Hahn, 1997). They may also be unable to communicate mental status changes such as anxiety, depression, illusions, hallucinations, and delusions which are frequently reported in GBS (Cochen et al., 2005; Sharshar et al., 2012). While treatment strategies exist to alleviate these complications, physicians depend on patients' reports in order to detect symptoms. When communication of symptoms becomes impossible, individuals suffer in silence. Thus, in our ICU, the standard of care for severe GBS is to sedate patients during the period of complete paralysis in an effort to ease anxiety, alleviate pain, and prevent posttraumatic stress disorder (Savard, Al Thenayan, Norton, Sharpe, & Young, 2009).

Here we describe two patients with severe GBS who, while they could still communicate with medical staff, refused the administration of sedation as they progressed to a *complete* locked-in state. Once locked-in, functional magnetic resonance imaging (fMRI) was used in an effort to establish communication with these patients as no alternative means of communication were available. The feasibility of fMRI as a communication tool has been previously assessed in healthy control subjects (Gabriel et al., 2015; Monti et al., 2010; Sorger et al., 2009; Sorger, Reithler, Dahmen, & Goebel, 2012). This technique has also been used to communicate with patients with chronic disorders of consciousness who, like those with severe GBS, lack the overt motor responses that are required for traditional forms of communication (Fernández-Espejo & Owen, 2013; Monti et al., 2010). In this report we evaluate the utility of fMRI as a means of communication in severe GBS in an effort to assess the patients' clinical condition and mental status.

5.2 Methods

5.2.1 Participants

5.2.1.1 Healthy Participants

Fourteen right-handed healthy participants (23 ±3 years, 9 males) took part in the study. Participants had no known neurological or psychiatric disease. All participants provided their written informed consent and were compensated for their participation. Ethical approval for the research study was obtained by the Health Sciences Research Ethics Board of Western University and all study procedures were performed in accordance with relevant guidelines and regulations.

5.2.1.2 Guillain-Barré Patients

Two completely locked-in patients participated in the study and written informed consent was obtained from their substitute decision makers.

Patient 1 was a 70 year old male who presented to hospital with progressive upper limb weakness over the course of 3 days at home. Following hospital admission the patient developed progressive respiratory weakness with dysarthria and dysphagia. He was admitted to our ICU 13 days after hospital admission suffering from respiratory failure and required mechanical ventilation. The patient had a lumbar puncture that showed elevated protein and an electromyography exam was consistent with an acute motor and sensory axonal neuropathy variant of GBS. The patient was treated with two courses of intravenous immunoglobulin in the first few weeks of illness. While the patient could still communicate with left eyebrow movement and lateral movement of jaw he repeatedly indicated that he did not want to be sedated if his condition progressed to a complete locked-in state. On Day 38 of admission to hospital, the patient lost all muscle movement for communication. Following more than 6 weeks of absent motor responses the neurocritical care team requested an fMRI to try to determine if the patient could still hear, as significant demyelination of the cranial nerves had occurred. Neurological examination revealed that the patient had become de-efferented with non-reactive pupils, absent corneal reflexes, no cough or gag reflex, and no respiratory effort. An initial fMRI scan was conducted to assess the extent of auditory processing and command following. Positive fMRI findings encouraged a follow-up fMRI exam 3 days later to determine if the patient could communicate using fMRI. Approximately one month following imaging, the patient had a return of reliable means of communication through eyelid blink and jaw movement. Unfortunately, a 6 month EMG and nerve conduction study revealed very little improvement suggesting the patient would ultimately be severely impaired with his activities of daily living. After extensive conversations between the patient's family and the clinical team, life sustaining therapies were withdrawn and the patient died 7 months following admission to hospital.

Patient 2 was a 74 year old male who presented to hospital with respiratory dysfunction, dysphagia, and ascending weakness which was predated by a viral illness. The patient was admitted to our ICU upon hospital admission for respiratory failure and required mechanical ventilation. While the patient's initial lumbar puncture was normal, an electromyography exam was consistent with an acute motor axonal neuropathy variant of GBS. He was treated with two courses of intravenous immunoglobulin in the first few weeks of illness. The patient also indicated that he did not want to be sedated as his condition progressed to a complete locked-in state. On Day 10 of admission to hospital the patient lost eye movement for communication. An fMRI exam was performed 2 days later (Day 12) to screen the patient for delirium and mental status changes, and collect information about his clinical condition. The patient regained eye movement 30 days following admission and currently (4 months from admission) continues with slow gradual improvement including consistent eye movement and weak head and shoulder movements.

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5.2.2 Stimuli

All stimuli were recorded by a male native English speaker and played through MRI compatible noise-attenuated headphones.

5.2.2.1 Hierarchical Auditory Task

In Patient 1, a hierarchical auditory paradigm, previously described (see Chapter 2), was first employed to determine the patient's ability to hear. Briefly, the paradigm was presented in an interleaved block design and consisted of four different auditory conditions: silence, signal correlated noise (SCN), pseudoword sentences, and complex narratives. Each condition was 30 seconds in length and repeated five times for a total of 10 minutes. To determine if basic sound perception remained intact in the patient, we compared the haemodynamic responses of all auditory stimuli conditions (SCN, complex language, and pseudoword sentences) to the silent baseline condition. To assess speech perception, we compared the speech conditions (complex language and pseudoword sentences) to the SCN condition. To determine if the patient could comprehend language, we compared the complex language condition to the pseudoword condition.

5.2.2.2 Imagery Tasks

Healthy control participants and both patients performed two mental imagery tasks, motor imagery and spatial navigation imagery, as previously described by others (Boly et al., 2007; Fernández-Espejo et al., 2014; Fernández-Espejo & Owen, 2013; Gibson et al., 2014; Monti et al., 2010; Owen et al., 2006). In the motor imagery task, participants were instructed to imagine playing a vigorous game of tennis in which they were to remain stationary but swing their arm back and forth to hit a ball over and over again. In the spatial navigation task, participants were instructed to imagine moving around the rooms their home and visualize everything they see when moving from room to room. Both paradigms were five and a half minutes in length and had an interleaved block design of 30 seconds of mental imagery alternating with rest periods.

5.2.2.3 Communication Tasks

Once mental imagery was established in each patient, multiple fMRI communication scans were employed. Prior to each scan a yes-or-no question was asked and the patients were instructed to answer the question by either performing motor imagery to convey a "yes" response, or spatial navigation to convey a "no" response. The communication scans were identical to the mental imagery scans, except the beginning of each imagery period was cued with the word "imagine" whereby the patient was asked to answer the question by imagining the task that corresponded to the response they wished to convey.

5.2.3 MRI acquisition

Imaging was performed on a Signa 1.5T Excite HDxt TwinspeedMRI system at the University Hospital LHSC (London Health Sciences Centre, London, Canada). The functional paradigms used a T2*-weighted single shot echo-planar imaging acquisition sequence was (TR = 2500ms, TE = 40ms, matrix size = 64 x 64, slice thickness = 5mm, in-plane resolution = 3.75mm x 3.75mm, flip angle 90°). Each volume comprised 30 contiguous (no gap) slices. A T1-weighted 3D-FSPGR pulse sequence was also obtained.

5.2.4 FMRI analysis

Image preprocessing and statistical analyses were conducted using Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm). Functional images were manually AC-PC reoriented, realigned to help correct for motion, co-registered to the structural images, normalized to the echo planar imaging template provided in SPM8 and smoothed using an 8mm FWHM Gaussian kernel. For the healthy control group, one-sample t-tests were performed on both mental imagery tasks to obtain the patterns of activity for the group at the whole-brain level, using a cluster-defining voxelwise threshold of p <.001 (uncorrected), followed by a whole-brain FDR-correction for significance using cluster extent, p <.05. Single-subject fixed effect analysis was used for both healthy participants and patients. Based on the general linear model (GLM), regressors for each paradigm were modelled to the canonical haemodynamic response function. For the hierarchical auditory task, regressors that corresponded to the presentation of silence, signal correlated noise, and the two speech conditions were created. In the mental imagery and communication scans, each scan was modelled as belonging to the mental imagery (motor or spatial navigation) or the rest condition. Movement parameters were included as covariates in all tasks. Single-subject results were thresholded at a peak voxelwise threshold p <.001, uncorrected followed by whole-brain FDR-corrected for multiple comparisons using cluster extent, p <.05. Given our strong anatomical a priori hypotheses, when no significant activation was observed at this level, the statistical threshold was reduced to an uncorrected $p < 0.001$ to exclude the possibility of failing to detect more subtle changes in the blood oxygen level-dependent (BOLD) signal due to this conservative approach (Gibson et al., 2014).

In a further quantitative analysis, a region-of-interest (ROI) approach was used to analyze brain responses in individual subjects during the mental imagery and communication scans. Subject-specific ROIs were defined as a 10mm sphere with the center coordinates at the peak voxel of the most strongly activated significant cluster found in the motor imagery and spatial navigation task, which represented the supplementary motor area (SMA) and the occipito-parietal junction (OPJ), respectively. These ROIs were used to test for significant activation in both mental imagery scans and the communication scans. The MarsBaR SPM toolbox (http://marsbar.sourceforge.net/) was used to generate ROIs and test the activations.

In the communication scans, a similarity metric previously described by Monti et al., (2010) was used to quantify how closely the activity in each communication scan matched either mental imagery localizer task in order to decode the patient’s response. The relative similarity was assessed according to the Euclidean distance whereby the activity within each scan was plotted within a two dimensional plane with the axes representing the activation within each ROI from the imagery localizer scans (SMA for tennis imagery, or OPJ for spatial navigation). The relative similarity for each communication response was derived from this formula:

Relative Similarity of Communication Scan to Tennis Imagery Localizer:

$$rs(C_i, TL) = 1 - \left(\frac{d(C_i, TL)}{d(C_i, TL) + d(C_i, NL)}\right)$$

Relative Similarity of Communication Scan to Spatial Navigation Localizer:

$$rs(C_i, NL) = 1 - \left(\frac{d(C_i NL)}{d(C_i, TL) + d(C_i, NL)}\right)$$

The relative similarity (rs) of a specific communication response (C_i) and each imagery localizer (tennis localizer, TL; and navigation localizer, NL) is equal to one minus the ratio of the distance between C_i and each imagery localizer, and the total distance between the communication question from the two localizers (with d(x,y) representing the Euclidean distance separating point x from point y).

5.3 RESULTS

5.3.1 Auditory Processing in Patient 1

Functional neuroimaging performed on Patient 1 was used to assess if he could perceive auditory stimuli because a neurological examination had revealed extensive cranial nerve damage. The hierarchical auditory task revealed significant neural responses to all three levels of task, similar to previous findings in healthy control participants (Figure 4.1).

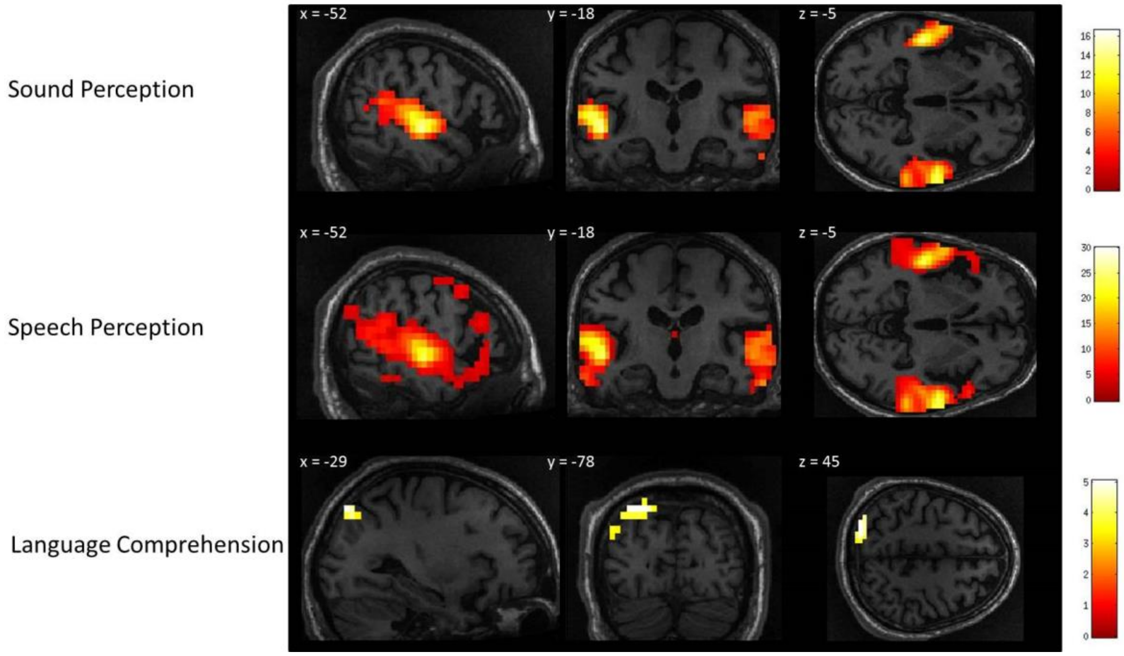

Figure 5.1. GBS Patient 1 results for the hierarchical auditory task. The top panel shows significant activation to the sound perception condition (sound>silence), the middle panel shows significant activation to the speech perception condition (speech>SCN), and the lower panel shows significant activation to the language comprehension condition (complex language>pseudoword sentences). Whole-brain results are displayed on slices where peak was observed and shown on the patient's T1 MRI image. Images are thresholded at a peak voxelwise threshold *p* <.001, uncorrected followed by whole-brain FDR-corrected for significance using cluster extent, *p* <.05.

In the sound perception condition, we found robust bilateral activation in the temporal cortex with peak activation observed in the posterior superior temporal gyrus centered on Heschl's gyrus, bilaterally. The speech perception condition revealed robust activation bilaterally in the temporal cortex of Patient 1 with greater spatial activation in the left temporal cortex extending outward from the posterior superior temporal gyrus to the angular gyrus, inferior temporal pole, and inferior frontal gyrus. The language comprehension condition which compared complex language to pseudoword sentences elicited left hemisphere dominant activation with peak activation observed in the left angular gyrus.

5.3.2 Mental Imagery Tasks

The motor imagery task (imagine playing tennis versus rest) elicited significant activation in the supplementary motor area for healthy volunteers. In Patient 1, motor imagery elicited significant activity in the supplementary motor cortex, primary motor cortex, precuneus, cerebellum, and left frontal pole. In Patient 2, motor imagery elicited significant activity in the supplementary motor cortex and primary motor cortex exclusively (Figure 5.2).

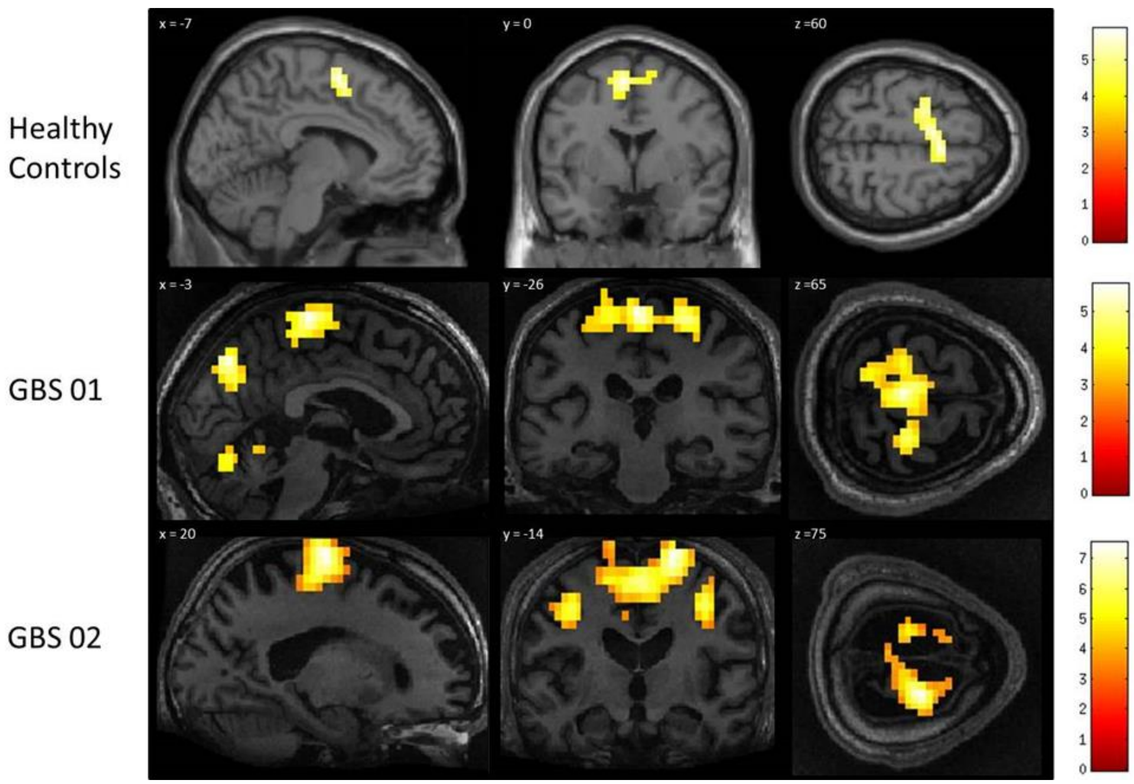

Figure 5.2. FMRI activation observed during the motor imagery task for a group of healthy participants (top panel) and two completely locked-in GBS patients (middle and lower panel). In healthy participants, a whole-brain group analysis revealed significant activation in the supplementary motor area, using a threshold of *p* < .05, FDR-corrected for multiple comparisons. Group analysis is shown on a canonical single-subject T1 MRI image. In both patients, extensive significant activation was observed in the supplementary and primary motor cortex. Patients' results are

displayed at a peak voxelwise threshold *p* < .001, uncorrected followed by whole-brain FDR-corrected for significance using cluster extent, *p* < .05 and displayed on their individual normalized T1 image.

Additionally, the extent of activity observed in the motor imagery task was within the bounds of normal variability found in the healthy volunteers (Figure 5.3).

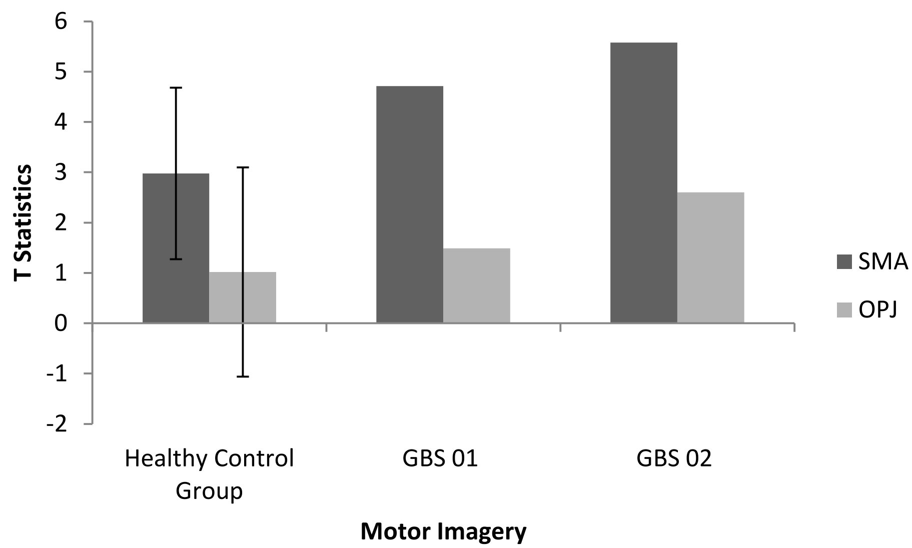

Figure 5.3. The patterns of activation in the regions-of-interest in the motor imagery task for both GBS patients and healthy controls. The error bars reflect the standard deviation of the healthy group. SMA = supplemental motor area, OPJ = occipito-parietal junction.

In healthy volunteers the spatial navigation task (imagine moving around the rooms of your house compared to rest) elicited significant activation in the occipito-parietal junction, cerebellum, parahippocampal gyrus, and left middle frontal gyrus. Similar to the healthy controls, significant activation of the occipito-parietal junction was observed in both patients (Figure 5.4).

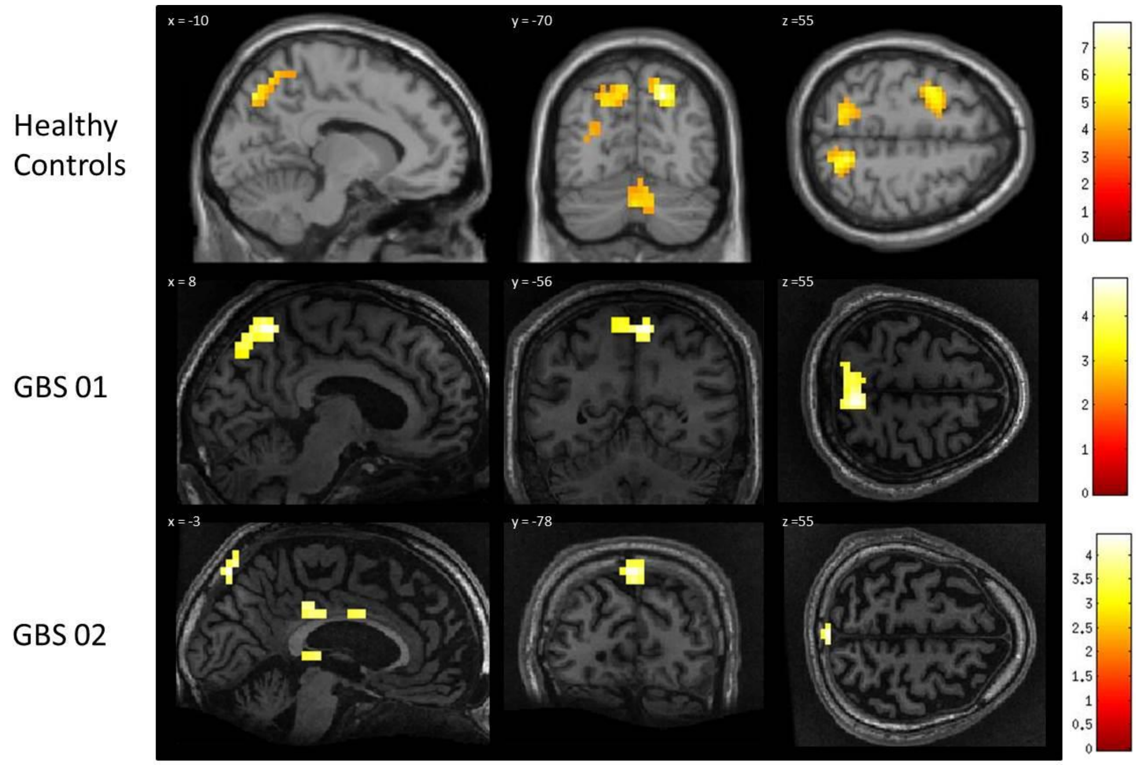

Figure 5.4. FMRI activation observed during the spatial navigation imagery task for a group of healthy participants (top panel) and two completely locked-in GBS patients (middle and lower panel). In healthy participants, a whole-brain group analysis revealed significant activation in the occipito-parietal junction, cerebellum, parahippocampal gyrus, and left middle frontal gyrus using a threshold of $p < .05$, FDR-corrected for multiple comparisons. Group analysis is shown on a canonical single-subject T1 MRI image. In patient 1 a whole-brain analysis revealed significant activation in the occipito-parietal junction with results displayed at a peak voxelwise threshold $p < .001$, uncorrected followed by whole-brain FDR-corrected for significance using cluster extent, $p < .05$ and displayed on the patient's normalized T1 image. Patient 2 had weaker activation in the occipito-parietal junction with results displayed at a peak voxelwise threshold of $p < .001$, uncorrected for multiple comparisons.

The extent of activity observed within the occipito-parietal junction during the spatial navigation task was also within the bounds of normal variability found in the healthy volunteers (Figure 5.5).

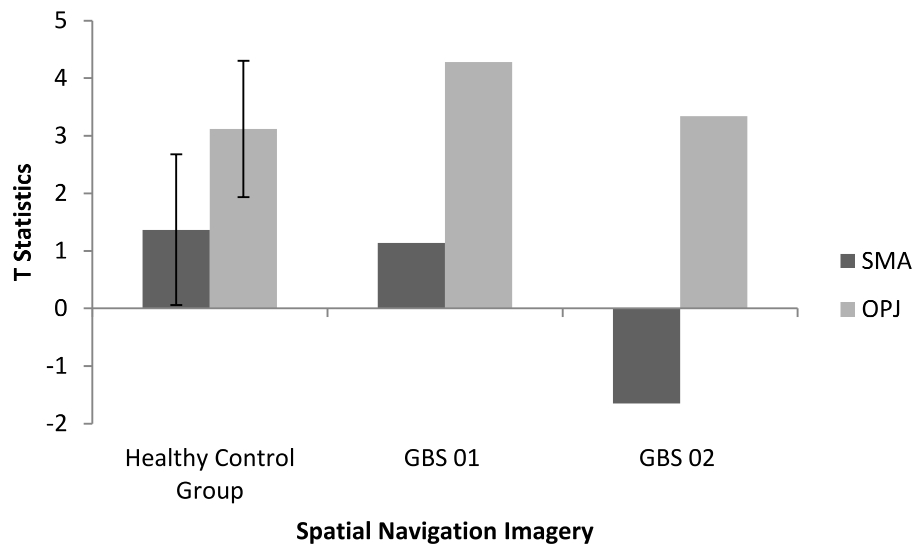

Figure 5.5. The patterns of activation in the regions-of-interest in the spatial navigation task for both patients and healthy controls. The error bars reflect the standard deviation of the healthy group. SMA = supplemental motor area, OPJ = occipito-parietal junction.

5.3.3 Communication Tasks

As both patients could relaibly perform the mental imagery tasks, these tasks then became surrogate markers of binary communication during a series of questions. For each question, both patients were instructed to perform motor imagery to respond ‘yes’ to the question or perform the spatial navigation task to respond ‘no’ to the question.

5.3.3.1 GBS Patient 1

In Patient 1’s functional neuroimaging scan, we evaluated four autobiographical questions to test self-identity and orientation in space, similar to previous communication attempts with non-responsive patients (Fernández-Espejo & Owen, 2013; Monti et al., 2010) . The neural activity oberserved in response to the first question, “Is your last name <incorrect name>?” closely matched that activity observed in the spatial navigation task indicating a correct ‘no’ response. The second question, “Is your last name <correct name>?” did not elicit activation in the peak ROI found in either mental imagery task. However, the patient did display robust significant activation bilaterally in lateral premotor cortex (BA 6) (Figure 5.6).

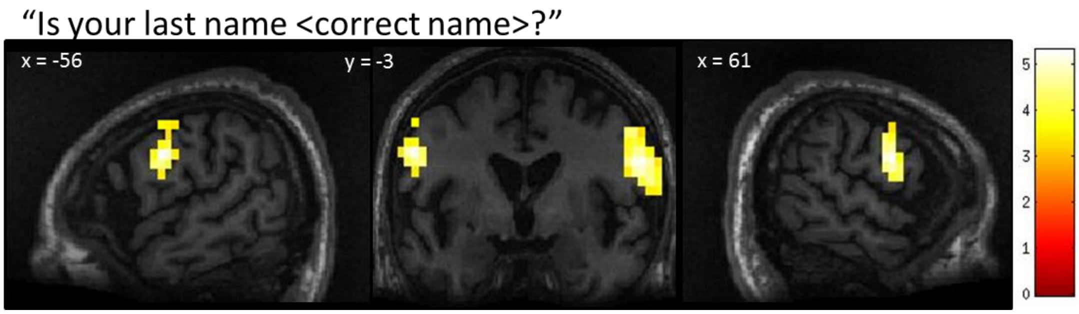

Figure 5.6. Patient 1’s whole-brain response to a question asking about his correct last name. Significant bilateral activation was observed in the lateral premotor cortex. Results displayed at a peak voxelwise threshold *p* <.001, uncorrected followed by whole-brain FDR-corrected for significance using cluster extent, *p* <.05 and displayed on the patient’s normalized T1 image.

The remaining two questions that pertained to orientation in space (“are you in the hospital?” and alternatively, “are you in the supermarket?”) did not yield statistically significant responses (Figure 5.7).

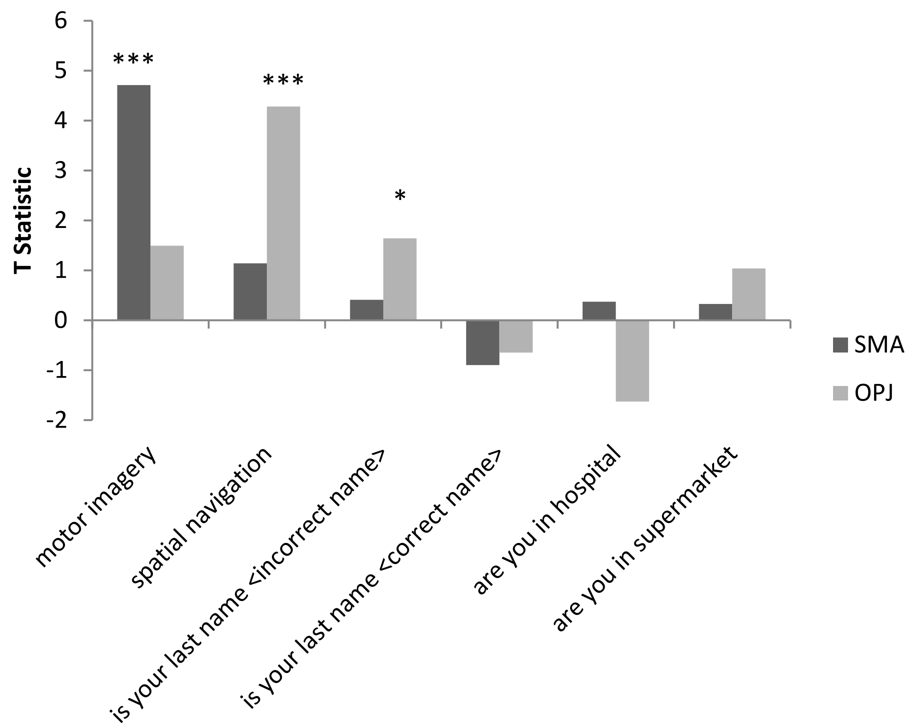

Figure 5.7. Patient 1's neural activation represented by *T* statistic graphs within the regions of interest (supplementary motor area (SMA) and occipito-parietal junction (OPJ)) for the mental imagery and communication tasks, ****p* **< 0.05, ******p* **< 0.001.

Using the relative-similarity analysis, the three questions that had activity observed within the regions of interest, produced a pattern of activation which matched the factually correct answer (Table 5.1).

Table 5.1. Relative similarity data for Patient 1. The pattern of neural activity that corresponds to the patient's answer for each question appears in boldface. Dashed lines indicate that no neural activity was observed in either ROI and the relative similarity cannot be computed.

	% Similarity to Localizers			
	Is your last name <incorrect name>?	Is your last name <correct name>?	Are you in the hospital?	Are you in the supermarket?
Motor Imagery Localizer = yes	38.9	----	**52.72**	43.13
Spatial Imagery Localizer = no	**61.1**	**----**	47.28	**56.87**

5.3.3.2 GBS Patient 2

In Patient 2's functional neuroimaging scan, seven autobiographical questions were asked to evaluate self-identify,orientation in space, disorganized thinking, and the patient's clinical condition. The patient had significant neural activity to three of the seven questions within the appropriate regions-of-interest. When asked, "do you feel safe?" the patient responded "yes," as activity observed matched activity found during the motory imagery task. Specifically, a significant response was found in the supplementary motor area (Figure 4.8). When asked "does one pound weigh more than two?" the patient incorrectly answered "yes," suggesting disorganized thinking (Figure 5.8). Similarly, when asked "is your last name <incorrect name>," the patient incorrectly answered "yes," suggesting problems with self-identity.

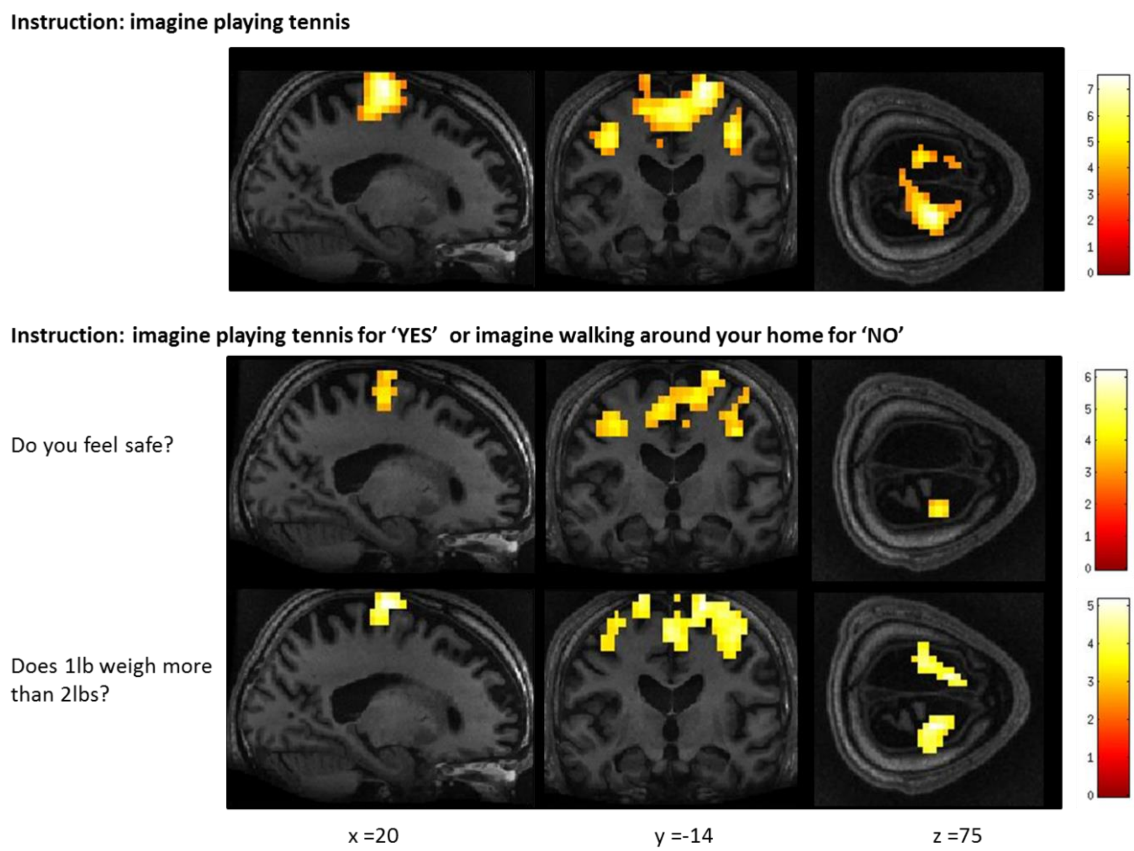

Figure 5.8. Whole-brain results from Patient 2 for the motor imagery task (top panel) and two communication scans (middle and lower panels). In the communcation scans (middle and lower panel), the patient's brain activity closely resembles that of the activity found in the motor imagery task (top panel) indicating a "yes" response to both questions. Results displayed at a peak voxelwise threshold *p* <.001, uncorrected, followed by whole-brain FDR-corrected for significance using cluster extent, *p* <.05 and displayed on the patient's normalized T1 image.

Quantitative analysis of each ROI within each communication scan confirmed that Patient 2 had robust statisitically significant responses to the three questions, similar to the motor imagery task (Figure 5.9).

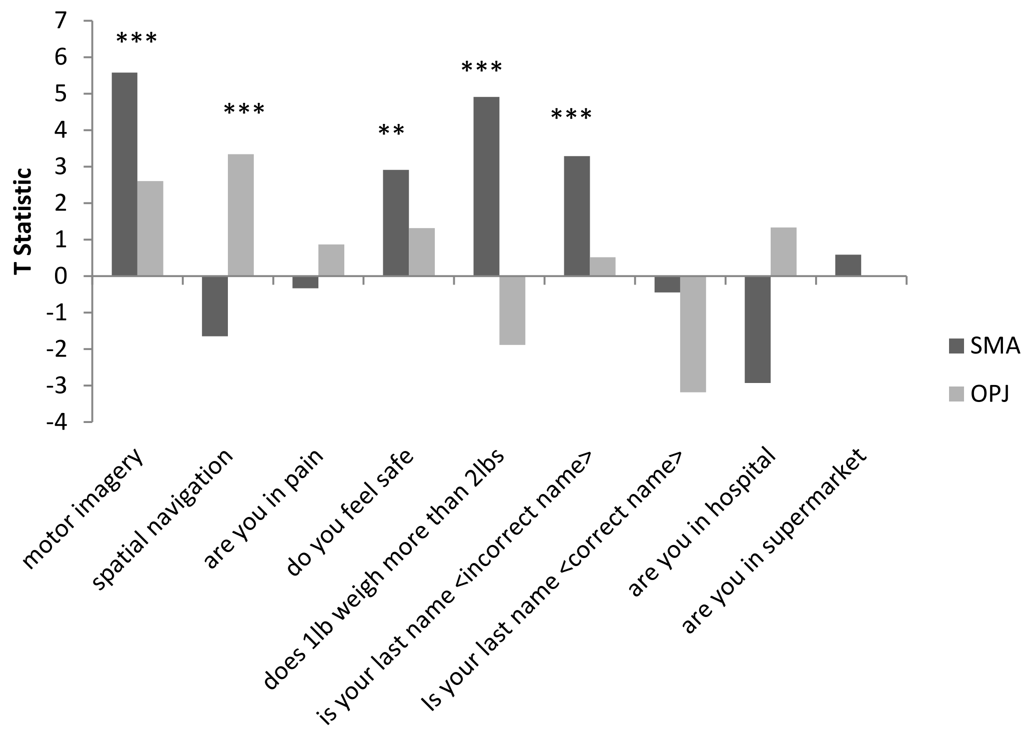

Figure 5.9. Patient 2's neural activity represented by T statistic graphs within the regions of interest (supplementary motor area (SMA) and occipito-parietal junction (OPJ)) for the mental imagery and communication tasks, *****p* < 0.005**, ******p*** < 0.001**.**

Three other questions ("are you in pain?," "are you in the hospital?" and "are you in the supermarket?") all yielded patterns of brain activity that indicated a "no" response but these results were not statistically significant (Table 5.2). When the patient was asked about his correct last name, "Is your last name <correct name>?" no activity in the peak ROIs or elsewhere at the whole-brain level was found.

Table 5.2. Relative similarity data for Patient 2. The pattern of neural activity that corresponds to the patient's answer for each question is boldface. Dashed lines indicate that no neural activity was observed in either ROI and the relative similarity cannot be computed.

	% Similarity to Localizers						
	Are you in pain?	Do you feel safe?	Does 1lb weigh more than 2lbs?	Is your last name <incorrect name>?	Is your last name <correct name>?	Are you in the hospital?	Are you in the supermarket?
Motor Imagery Localizer = yes	31.26	**62.75**	**64.92**	**64.77**	---	21.69	41.65
Spatial Imagery Localizer = no	**68.74**	37.25	35.08	35.23	**---**	**78.31**	**58.35**

5.4 Discussion

In this study, we used fMRI as a tool to assess hierarchical language processing, detect covert command following, and facilitate binary communication in two GBS patients who had total paralysis, mimicking complete locked-in syndrome. In Patient 1, a hierarchical auditory task established that the patient retained auditory processing, indicating that the vestibulocochlear nerve retained a certain level of functioning. Intact auditory processing was important to determine, as other cranial nerves showed significant damage during neurological examination. Additionally, both patients were able to perform the two mental imagery tasks which indicated that they could willfully modulate their brain activity when instructed, similar to healthy control individuals. This suggests that both patients retained awareness, and the ability to understand language and follow instructions. Most importantly, because of their ability to successful perform the two mental imagery tasks, we were able to use this technique to facilitate communication with both patients.

In Patient 1, we employed four questions that assessed self-identity and orientation in space, which have been previously used to establish communication in non-responsive patients (Fernández-Espejo & Owen, 2013; Monti et al., 2010). When the patient was asked if his last name was an inaccurate last name, a significant neural response was detected in OPJ, similar to the spatial navigation localizer, indicating that he was responding “no.” In the correct name trial, we did not observe any activity in peak mental imagery areas; however, we did note significant robust activation in the lateral premotor area (BA 6), which is known to be involved in imagined hand movements, suggesting that the patient was likely attempting to answer “yes” (Gerardin et al., 2000; Guillot et al., 2008; Lotze & Halsband, 2006). We hypothesize that the motor imagery response to this question was different than the initial motor imagery localizer (SMA) because the patient might have used a different strategy to perform the imagery task as the communication scans occurred a few days following the initial mental imagery tasks. Additionally, just prior to the communication scan the patient was given 0.5 mg of hydromorphone to potentially alleviate some discomfort while being imaged. While this dosage had not affected communication responses previously in the patient when he had been behaviorally responsive, a decrease in neural responses was observed for the remaining questions. The administration of the analgesic may have altered the patient’s ability to follow the task instructions and sustain the mental imagery over multiple blocks thus decreasing our ability to detect a robust response. However, although the response was non-significant, the pattern of activation matched the factually correct answer in all questions.

The successful communication trial in Patient 1 prompted us to repeat the communication trial in Patient 2 and to also include questions that were relevant to the patient’s clinical condition and quality of life. In Patient 2, we found significant neural responses to three questions; however, the patient incorrectly answered two of these questions. When asked “does one pound weigh more than two?” the patient incorrectly answered “yes”. This question was taken from the Confusion Assessment Method for the

Intensive Care Unit (CAM-ICU) assessment for delirium (Ely et al., 2001). Incorrectly answering this question suggests that the patient may have disorganized thinking. Similarly, when asked "is your last name Johnson?" the patient incorrectly answered "yes," suggesting problems with self-identity. Taken together, this suggests that the patient could have been experiencing mental status abnormalities. Such abnormal mental statuses are known to occur in upwards of 31% of GBS cases (Cochen et al., 2005). We also asked Patient 2 if he felt safe, a question that has no known factual response but solely relies on the patient's report. This question is often posed by psychiatrists to understand if a patient is experiencing any paranoid delusions, which have also been reported in GBS (Cochen et al., 2005). A significant neural response that matched the motor imagery localizer was detected, indicating an affirmative response that the patient indeed felt safe suggesting that he was not currently experiencing paranoia.

5.4.1 Implications for Clinical Management of GBS

Our study suggests that fMRI holds promise as a reliable communication tool which may improve clinical care in *complete* locked-in patients within the ICU. Communication through fMRI can allow patients to convey information about their welfare that relates to their clinical condition and quality of life. Determining how a patient is coping with their illness can help clinicians determine what interventions may improve a patient's welfare (Graham et al., 2015). Specifically, the use of fMRI for communication could allow a patient to convey the presence and severity of pain which then would allow for pharmacological interventions such as the administration of gabapentin or carbamazepine (Pandey et al., 2005). Similarly, affirmative responses in regard to symptoms of psychiatric complications can allow for medical treatment which could include selective serotonin reuptake inhibitors for anxiety and depression (Brousseau, Arciniegas, & Harris, 2005) or neuroleptic agents for delusions and hallucinations (Harms, 2011).

FMRI communication paradigms could also be used as a screening tool for a more objective assessment of symptoms instead of relying upon direct report from the patient. For example, clinicians could assess the patient for the presence and extent of delirium using modified features from the CAM-ICU. A positive delirium screen could inform clinicians about the most appropriate treatment. Additionally, fMRI could be used to assess decision-making capacity which then could allow the patient to participate in their own medical decision making. A modified version of the Mini-Mental State Examination has been recently proposed to assess a patient's decision-making capacity during fMRI imaging (Peterson et al., 2013). Importantly, Peterson et al., (2013) noted that once decision-making capacity has been established, a patient may only be able to be involved in their own medical decision making in circumstances where potential benefits outweigh or are equal to the harms relative to alternative treatments. In the acute clinical context, these questions might be limited to the administration of analgesics. Importantly, these simplistic binary responses may not be appropriate for high stakes situations such as end-of-life decision-making (Fins & Schiff, 2010).

5.4.2 Limitations

Using fMRI, we could not detect a response to some questions that were posed to the patients. In some communication trials no neural response was detected or the response was not robust enough to reach statistical significance. It is not clear why the patients were unable to convey an answer to every question, although this has also been found in other behaviorally non-responsive patients (Fernández-Espejo & Owen, 2013; Monti et al., 2010) and healthy volunteers (Gabriel et al., 2015). Possibly they did not understand or recall the question that was asked at the beginning of the trial to an extent that allowed them to form a response, or they may have lacked the ability or motivation to sustain the response through the duration of the trial. Thus, future research should be selective about which questions are asked of patients as fatigue is likely to be a limiting factor. Others have suggested imaging should be kept to a maximum of 60 minutes in duration (Fernández-Espejo & Owen, 2013; Weijer et al., 2015) which would allow for 10 questions. Additionally, while serial scanning may be useful for continuing to assess a patient's well-being, repetitive intra-hospital transport to MRI may result in an increased risk of adverse events and so only the most important clinical questions should be evaluated when the need arises (Weijer et al., 2015). Most importantly, negative fMRI results should never be interpreted as evidence of an *absence* of preserved awareness as false negative fMRI findings are known to occur, even in healthy volunteers (Owen et al., 2007; Owen & Coleman, 2007).

5.4.3 Future Directions

While the mental imagery tasks employed in this study are the best-established fMRI techniques for communication with behaviorally non-responsive patients, future studies that seek to communicate with such patients may benefit from employing different approaches. For example, some selective attention tasks are better at detecting responses in healthy volunteers while also reducing the required imaging time (Naci et al., 2013). However, the high cost of fMRI and its lack of portability may limit its use in severe GBS patients who require long term solutions for communication. Other noninvasive functional neuroimaging techniques, such as EEG and functional near-infrared spectroscopy (fNIRS), are more portable and less expensive solutions. EEG has shown promise as a bedside communication tool in disorders of consciousness (Cruse et al., 2011; Lulé et al., 2013) and typical locked-in syndrome (Bai et al., 2008; Felton, Radwin, Wilson, & Williams, 2009; Kübler & Birbaumer, 2008; Mugler, Ruf, Halder, Bensch, & Kübler, 2010; Sellers & Donchin, 2006), however, *complete* locked-in patients have not been able to communicate via EEG (Kübler & Birbaumer, 2008). FNIRS is a relatively new technology but holds promise as a portable and reliable communication tool in *complete* locked-in syndrome (Abdalmalak et al., 2016; Chaudhary, Xia, Silvoni, Cohen, & Birbaumer, 2017; Gallegos-Ayala et al., 2014).

Finding a reliable means of communication at the bedside that does not rely on a behavioral response could improve the quality of life for many ICU patients beyond severe GBS patients. These may include patients suffering from critical illness polyneuropathy/myopathy, a syndrome characterized by severe muscle weakness, which occurs in at least 25-50% of ICU patients (Green, 2005; Latronico & Bolton, 2011). These types of brain-computer interfaces which circumvent physical disabilities in patients can aid in proper clinical management and may prevent unnecessary medical tests, thus conserving scarce resources. As a specific example, Patient 1 was taken for multiple urgent CTs over the course of his time in the ICU to rule out a catastrophic intracerebral injury because behavioral communication at the bedside was lost unexpectedly on multiple occasions. However, the CT images would prove to be negative and his motor responses would always subsequently improve the following day or several days later. The patient was likely experiencing fluctuating levels of muscle weakness and not the loss of awareness. A brain-computer interface could identify this distinction and urgent diagnostic imaging would not be required.

GBS may also provide unique insights into how patients perceive the use of BCIs. With a relatively low mortality rate (3-13%) (van den Berg, Bunschoten, van Doorn, & Jacobs, 2013), a large proportion of GBS patients eventually recover oral communication which would allow for semi-structured interviews where patients could describe their experience with a BCI and researchers could learn how improvements could be made.

5.5 Conclusion

In this study we demonstrate that it is feasible to use fMRI as a communication tool for severe GBS patients. We suggest that functional neuroimaging can be used in the ICU setting to ask patients about their clinical condition and quality of life. Specifically, in regards to GBS patients, fMRI can allow the medical team to ask if pain is being adequately managed and if patients are experiencing any distress. Responses to these questions could then allow for treatment solutions. Additionally, neuroimaging could assess delirium and decision-making capacity, and allow patients to be involved in their own medical decisions.

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Chapter 6

6 General Discussion

6.1 Key Findings

While a considerable amount of functional neuroimaging research has shed light on the cerebral function of patients in chronic disorders of consciousness, little is known about the utility of these methods in the acute stage of coma. The research presented in this thesis sought to determine if it was feasible to carry out fMRI investigations in critically ill patients and to establish whether such research possesses any diagnostic or prognostic value. To accomplish this, a hierarchically designed approach was used to interrogate residual cognitive function in the auditory domain (Figure 6.1). Similar to hierarchically conducted studies in VS patients (Coleman et al., 2009; Coleman et al., 2007; Owen et al., 2005, 2006; Owen et al., 2005), this research assessed auditory processing starting with the simplest forms of perception and proceeded successively to more complex cognitive functions. This systematic approach allowed for the assessment of sound perception, speech perception, language comprehension, command following, and ultimately, communication. Importantly, this framework is able to characterize the extent of preserved cognition and delineate where the breakdown in cognitive processing occurs in severely brain injured individuals. It is unclear where awareness emerges along this hierarchical structure, although research in anesthesia suggests that higher level semantic processes that support language comprehension do not occur in the absence of awareness (Adapa et al., 2014; Davis et al., 2007). This evidence indicates that awareness must precede language comprehension along this continuum.

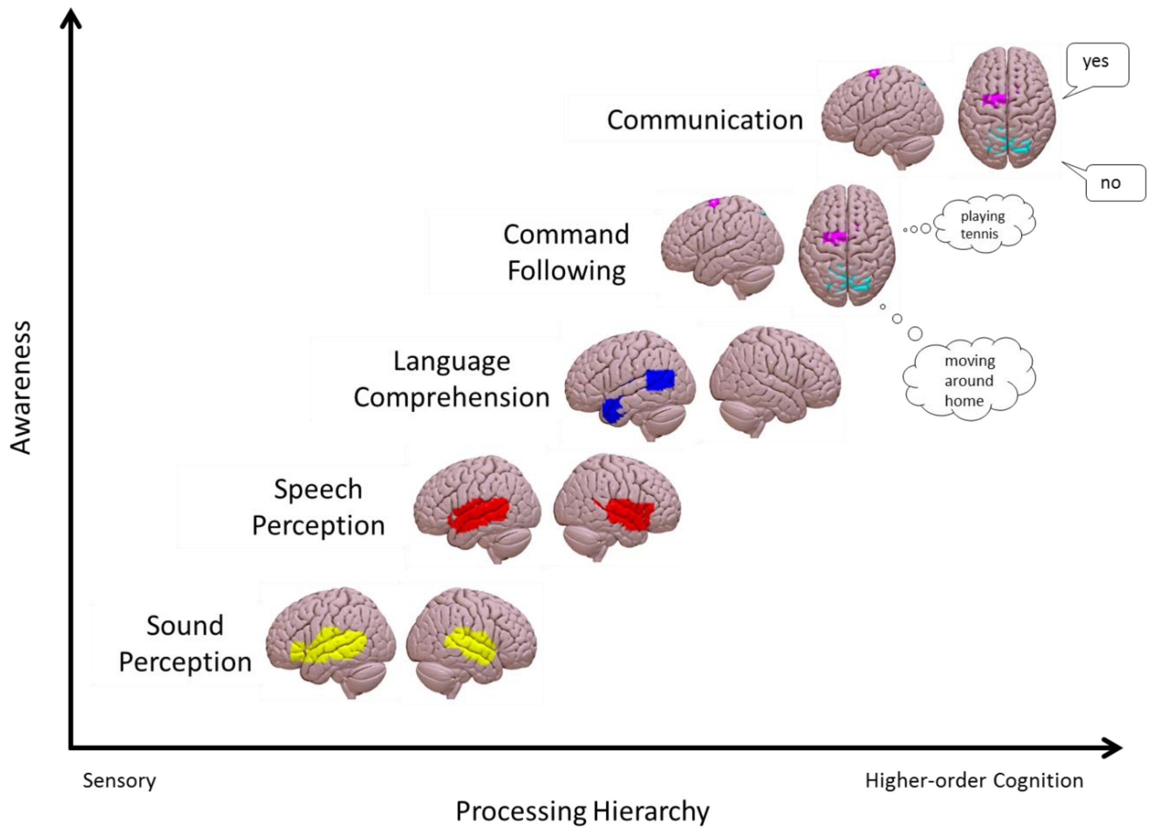

Figure 6.1. Hierarchical approach for the use of fMRI to interrogate residual cognitive function in the auditory domain.

In Chapter 2, we developed and assessed the reliability of three versions of a hierarchically-designed auditory task to detect sound perception, speech perception, and language comprehension in individual healthy participants, in order to determine whether this same procedure could be used in comatose patients. In control volunteers, reliable single-subject activations were found for both sound and speech perception contrasts, but not for language comprehension, using a clinical 1.5 T scanner. These findings indicated that a hierarchical auditory task could be used to identify whether a critically ill patient has intact sound and speech perception using a lower-field strength scanner in a hospital setting. Subsequently, the task was applied in two acutely comatose patients. Evidence was found for sound perception, speech perception, and language comprehension in one comatose subject who, subsequently, had full functional recovery. On the other hand, a minimal response to only the lowest-level sound perception contrast was observed in the individual who succumbed to their injury.

The preliminary findings in Chapter 2 demonstrated that it was feasible to interrogate cognitive function in coma and prompted the experiment in Chapter 3, which examined the relationship between auditory processing and outcome in a larger cohort of patients. Chapter 3 established that a large proportion of comatose individuals retained perceptual auditory abilities while a minority of subjects also had preserved higher-order language comprehension. Notably, the extent of auditory processing in coma was associated with an individual's level of functional recovery. These findings suggest that functional neuroimaging techniques that interrogate brain function in a hierarchical manner can provide additional prognostic information in coma. Reliable and objective indicators of positive recovery following coma are urgently required as current clinical tools are only able to determine when patients will have a poor outcome. When indicators of poor outcome are absent, clinicians are unable to accurately predict the course of recovery from coma and are required to rely on their subjective judgement and experience when making estimations of the likelihood of expected recovery. In the ICU, these estimations are often used in making decisions about the removal of life sustaining therapy. Currently, there is high variability in the prevalence of withdrawal of therapies between countries, within countries, and even between clinicians in the same hospitals (Mark, Rayner, Lee, & Curtis, 2015). These differences are guided by individual perceptions of neurological prognosis (Turgeon et al., 2013). However, many decisions to withdraw life support are likely made too early, often within the first three days of care, which can be too soon for accurate neuroprognostication (Turgeon et al., 2011). Objective measures that can accurately predict cognitive recovery in the first few weeks following brain injury could prevent early removal of life supporting measures (Young & Owen, 2014). Further research should continue to elucidate the role of fMRI as an indicator of positive outcome following coma which could be used to complement current clinical tools and aid prognostication.

In Chapter 4, we sought to determine if comatose patients could retain higher levels of awareness than can be detected through behavioural examination at the bedside. FMRI investigations have revealed that aspects of higher order language comprehension are detectible in a proportion of comatose patients (Chapter 3), suggesting that they may retain higher levels of awareness than can be detected through behavioural examination. However, because the task was passive in nature, as it required no participation on the part of the patient, these neural responses may be entirely automatic. Therefore it is difficult to ascertain whether the observed activity is a reflection of *conscious* experience or rather, is generated subconsciously. Therefore, in Chapter 4, an *active* task was used in an attempt to find unequivocal evidence of volition and awareness in coma. This investigation used two mental imagery tasks that have been previously used to demonstrate covert command following ability in some VS patients (Monti et al., 2010; Owen et al., 2006). Of 6 patients who demonstrated higher level language comprehension, 5 were unable to perform mental imagery; however, remarkably, one comatose patient was able respond to the task instructions by modulating his brain activity, confirming that he was consciously aware of his environment. This presents a direct challenge to his previous behavioural examination, which was unable to detect any signs of awareness, suggesting that fMRI could aid in the diagnosis of coma and identify early markers of awareness. Additionally, functional neuroimaging may be a superior tool with which to assess the depth of coma in comparison to clinical examination. Clinical examination is susceptible to variability in observer reports of responses to external stimuli, whereas the nature of functional neuroimaging effectively eliminates this variability in observational reporting by offering objective measures to assess the depth of coma. In fact, functional neuroimaging techniques have been shown to be superior to even the most extensive clinical investigations in specialized centers in their ability to detect awareness in patients with chronic disorders of consciousness (Cruse et al., 2011; Fernández-Espejo & Owen, 2013; Monti et al., 2010; Naci & Owen, 2013; Owen, et al., 2006; Bardin et al., 2011). Importantly, finding signs of covert awareness earlier in the course of injury might allow for timelier implementation of intensive rehabilitation which could maximize functional outcomes (Maulden, Gassaway, Horn, Smout, & DeJong, 2005; Zhu, Poon, Chan, & Chan, 2007).

By convention, arousal is thought to be a prerequisite for awareness (Young, 2009). That is, one must be awake to have a conscious experience. However, the finding of intact awareness in coma in Chapter 4 indicates that the two major dimensions of consciousness could be dissociable components. Examples in sleep, such as sleep walking (for review see, Bassetti, Vella, Donati, & Wielepp, 2000), the incorporation of stimuli into dream content (Burton, Harsh, & Badia, 1988), and lucid dreaming (for review see, Stumbrys, Erlacher, Schädlich, & Schredl, 2012) are an indication that some forms of awareness occur in the absence of arousal. Additionally, event related potentials that relate to higher-order processing such as attentional responses and semantic analysis of auditory stimuli have been identified in sleep (Bastuji, Perrin, & Garcia-Larrea, 2002; Chennu & Bekinschtein, 2012; Cote, 2002). From a purely scientific standpoint, novel research exploring residual cognition in the absence of arousal, such as coma, will provide unique insight in identifying the neural correlates of consciousness and inform theoretical perspectives of consciousness.

In addition to its importance as a device for identifying covert awareness in coma, the use of fMRI can be extended even further as a communication tool. In Chapter 5 we demonstrated that two non-responsive, critically ill patients diagnosed with severe Guillain-Barré syndrome (GBS) could communicate their thoughts solely through modulating their brain activity. Both individuals were able to use two mental imagery tasks to convey answers to binary questions, giving us insight into their internal state. Thus, this research posits that functional neuroimaging methods could be implemented as a delirium screening tool and used to assess decision-making capacity in overtly non-responsive patients within the ICU. This augmentative communication tool could allow patients to be involved in their own medical decision-making.

6.2 Challenges and Limitations

There are numerous challenges that arise in implementing fMRI as a clinical tool in critically ill patients. Principally, the medical fragility following an acute brain injury can impede imaging, thus limiting the use of fMRI in a considerable proportion of the population. Only those who are hemodynamically stable and at low risk for deterioration should participate in imaging studies. Patients with increased intracranial pressure and congestive heart failure who are unable to lie flat in the scanner should be excluded from research. Additionally, subjects with electronic implants such as pacemakers, brain aneurysm clips, Swan Ganz catheters, and foreign metal objects (e.g. gunshot wound) are unable to go into the imaging suite. Moreover, individuals who require large amounts of sedation should also be excluded from study as the effects of anesthetic agents may affect the BOLD signal. Once eligibility and consent has been obtained, the scheduling and organization of imaging should be done promptly as both the medical stability and level of consciousness in acute patients can change over a period of hours or days.

The interpretation of fMRI data may also be complicated by structural insults to the brain, such as injuries that result in midline shift, trauma that requires bone flap removal, and gross hydrocephalus. These types of injuries may prevent the normalization of the images to a reference image of a healthy brain, which would result in the inability to relate the subject’s brain activity to normal patterns of activity found in standard stereotaxic space (Owen & Coleman, 2007). Moreover, it is unclear what effect acute vascular injuries such as intracranial bleeding and stroke would have on the BOLD signal.

In this thesis, I have attempted to demonstrate a number of ways in which optimization of imaging procedures in critically ill patients can mitigate some of these risks. First, these investigations have validated that fMRI imaging is sensitive enough to detect single-subject brain activity on lower field strength 1.5T clinical hospital scanners. This is important, because these are the types of scanners that are most commonly found in clinical settings (as opposed to the more powerful 3T scanners, on which most of the previous research has been completed with). Ensuring that imaging is conducted within a hospital setting is essential for critically ill patients where rapid response teams including intensivists, ICU nurses, and respiratory therapists are available if a serious adverse event was to occur within the imaging suite. Additionally, whenever possible, it is suggested that patients should be imaged in conjunction with clinically indicated structural scanning in order to decrease the risks associated with multiple intra-hospital transports (Weijer et al., 2015) .

However, some empirical challenges with employing neuroimaging methods in the diagnosis and prognosis of acutely comatose patients remain. If fMRI findings were to be considered in decisions to continue or withdraw life sustaining therapies, both false negative and false positive findings could have grave consequences (see Peterson, Cruse, Naci, Weijer, & Owen, 2015). A false negative finding, or an inability to detect cognitive function although it persists, could be interpreted as evidence of severe impairment and lead to the premature withdrawal of life sustaining therapies. However, we argue that the absence of significant findings should never be interpreted as an absence of preserved cognition, as false negative findings are known to occur, even in healthy volunteers (Fernández-Espejo et al., 2014; Gabriel et al., 2015). Alternatively, false positive findings, where fMRI results incorrectly indicate that cognitive function is present, could result in a missed “window of opportunity” to withdraw life sustaining therapies (Wilkinson, 2011). Comatose subjects usually regain the ability to breathe on their own without the support of mechanical ventilation within a few weeks from injury, regardless of eventual outcome. Some of these patients, although no longer requiring life support, will survive indefinitely with a severe disability. Therefore, accurate prognosis needs to be made during this time-sensitive period, in order for end-of-life decisions to be made appropriately, as these decisions are unlikely to be made, after the subject has endured beyond the need for life support. Moreover, it is challenging to evaluate a prognostic tool that may indicate good recovery when treatment withdrawal decisions occur and one cannot determine the actual mortality rates. The true validity of the novel test cannot be established but only how well it is in agreement with other prognostic tools which influence the continuation or withdrawal of life support.

6.3 Future Directions

Research examining residual cognitive function in acute coma is lacking. This thesis has demonstrated that fMRI holds promise for improving the accuracy of both the diagnosis and prognosis of acutely brain injured patients. While these investigations included a small cohort of subjects, this dissertation has revealed valuable potential for future clinical trials to evaluate the use of fMRI in critical illness. These investigations should include large, longitudinal, and multicentre studies to reach definitive conclusions about optimal, efficient, and reliable testing. Importantly, longitudinal studies that examine changes in cortical responses of brain-injured patients in repeated assessments should correlate those findings to functional recovery in the hope that they will delineate early patterns of brain activity that may predict the subsequent extent of disability in survivors. Moreover, research examining prognostic utility should be carried out in countries with a low prevalence of withdrawal of life-sustaining treatment to understand the true specificity and sensitivity of functional neuroimaging techniques.

Another promising avenue for research is the continued efforts to find portable bedside solutions for assessing residual cognitive function. This is paramount in cases where patients are precluded from imaging due to implanted ferromagnetic objects or where there is a high risk of deterioration during transport to the imaging suite, both of which are common limitations in acutely brain injured patients. Electroencephalography (EEG) is one technique that can be used in patients with metallic implants where recordings can be obtained at the bedside. EEG is a measure of changes in the brain's electrical activity and has been used to evaluate responses to a variety of stimuli, such as sounds and words as well as volitional responses to verbal instructions (e.g. imaging squeezing your hand). EEG paradigms have been used to demonstrate attention-orienting responses (Bekinschtein et al., 2009; Faugeras et al., 2011; Gibson et al., 2016) and even covert awareness (Cruse et al., 2011) in a small proportion of patients with chronic disorders of consciousness. Recently, auditory discrimination, as detected by EEG, has been found to be predictive of awakening in post-anoxic coma (Rossetti et al., 2014; Tzovara et al., 2013, 2016; Tzovara, Simonin, Oddo, Rossetti, & De Lucia, 2015) demonstrating that EEG may have potential for use in prognosticating outcomes of comatose survivors of cardiopulmonary resuscitation. However, the use of EEG to examine covert awareness in acute coma may not be effective as it shows far reduced sensitivity compared to fMRI in healthy volunteers (Cruse et al., 2011; Gabriel et al., 2015). Alternatively, functional near-infrared spectroscopy (fNIRS), a relatively new portable technology, might be a suitable alternative for fMRI as it allows for non-invasive hemodynamic measures of cortical activity (Naci et al., 2012). Research has shown that fNIRS has a similar sensitivity as fMRI in detecting awareness with mental imagery tasks in healthy controls (Abdalmalak et al., 2016). Recently, fNIRS has been successfully used to decode neural responses in complete locked-in patients and is likely the most promising way forward in the development of brain-computer interfaces which can allow for communication with non-responsive patients (Chaudhary, Xia, Silvoni, Cohen, & Birbaumer, 2017).

Finally, implementation of functional neuroimaging tools that can provide superior insight into the extent of recovery of patients may significantly shape future medical management and interventions. Critically, identifying residual cognitive function early in the course of injury might allow for the application of novel brain stimulation techniques which could improve recovery. Although in the initial stages of research, some neuromodulary treatments that are known to enhance the excitability of thalamic efferent neurons have shown encouraging results in chronic disorders of consciousness (for review see Thibaut & Laureys, 2015). Case reports of transient behavioural improvements in awareness have been reported in chronic patients after the administration of repetitive transcranial magnetic stimulation (Pape et al., 2009; Manganotti et al., 2013; Piccione et al., 2011), transcranial direct current stimulation (tDCS) (Thibaut, Bruno, Ledoux, Demertzi, & Laureys, 2014), and ultrasonic thalamic stimulation (Monti, Schnakers, Korb, Bystritsky, & Vespa, 2016). Moreover, deep brain stimulation of the thalamic intralaminar nuclei has also been found to improve behavioural responsiveness in a minimally conscious subject who received the intervention six years following injury (Schiff et al., 2007). It remains to be investigated whether earlier interventions would lead to better and more permanent increases in behavioural responsiveness. The most optimistic forecast of the state of affairs in the next 20 years in the field of disorders of consciousness would be a lower incidence of patients living in such severely disabled states as a result of early detection of residual cognitive function which will lend itself to early interventions and treatments.

6.4 References

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Appendices

Appendix A: Ethics approval.

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Annual Continuing Ethics Approval Notice

Date: September 09, 2016
Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology,Western University

Review Type: Full Board
HSREB File Number: [redacted]
Study Title: A Multi-Modality Approach to Study Cerebral Responses in Comatose Patients (REB #18454)
Sponsor: Canadian Excellence Research Chair

HSREB Renewal Due Date & HSREB Expiry Date:
Renewal Due -2017/09/30
Expiry Date -2017/10/04

The Western University Health Science Research Ethics Board (HSREB) has reviewed the Continuing Ethics Review (CER) Form and is re-issuing approval for the above noted study.

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 (ICH E6 R1), the Ontario Freedom of Information and Protection of Privacy Act (FIPPA, 1990), 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]

Curriculum Vitae

Name:	Loretta Norton
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2011-2017 Ph.D. Candidate
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	Brock University St. Catharines, Ontario, Canada 2003-2008 B.Sc.
Honours and Awards:	Canadian Institutes of Health Research Doctoral Award 2012-2015
	Nellie Farthing Fellowship in the Medical Sciences 2013
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	Ontario Graduate Scholarship Doctoral Fellowship 2009-2010
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Research Assistant, Movement Disorders Laboratory
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