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I am submitting herewith a dissertation written by Christopher Richard N. Nicholas entitled "Functional Neuroimaging in a Pediatric Case of Impaired Awareness." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

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Dean of the Graduate School

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Functional Neuroimaging In a Pediatric Case of Impaired Awareness

A Dissertation
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Doctor of Philosophy
Degree
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Abstract

Disorders of consciousness (DOC) occur in severe cases of neurological disease and acquired brain injury, spanning the continuum from complete unresponsiveness (vegetative state) to partial conscious awareness with only erratic voluntary behavioral responses (minimally conscious state). Assessing the patient's level of awareness of self and their environment through behavioral evaluation is notoriously difficult and may lead to misdiagnosis if residual cognitive function goes undetected. A number of studies (Di et al., 2007; Staffen et al., 2008; Coleman et al., 2007; Qin et al., 2010) applying brain-imaging methods to measure brain activity associated with processing self-referential stimuli (stimuli related to the self) have found similar responses between patients with DOC and healthy volunteers. The present study involved a unique pediatric patient with comorbid quadriplegia and non-communicative impaired awaress who underwent fMRI to explore brain activity associated with the auditory presentation of personally relevant language stimuli: the subject's own name (SON) and a familiar voice (FV). Activation was observed in the left tranverse temporal gyrus across all auditory stimuli. Presentation of the SON revealed activation in the left ventromedial prefrontal cortex (vMPFC) and right dorsolateral prefrontal cortex (DLPFC) and presentation of the FV revealed activation in the left supramarginal gyrus. These findings provide evidence of preserved brain activity in this patient during the presentation of self-referential stimuli and therefore support the application of functional neuroimaging methods to detect residual brain activity in pediatric patients who display impaired awareness.

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Abbreviations

ACC	Anterior cingulate cortex
AUD	Auditory
BA	Brondmann area
BOLD	Blood-oxygen-level-dependent
CMS	Cortical midline structures
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
DOC	Disorders of consciousness
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
FV	Familiar voice
LIS	Locked-in syndrome
MCS	Minimally conscious state
MOPFC	Medial orbital prefrontal cortex
MPC	Medial parietal cortex
MPFC	Medial prefrontal cortex
MTG	Middle temporal gyrus
PCC	Posterior cingulated cortex
PET	Positron emission tomography
PVS	Persistent vegetative state
RSC	Retrosplenial cortex
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SON	Subject’s own name
SRP	Self-referential processing
UN	Unknown name
UV	Unfamiliar voice
vMPFC	Ventromedial prefrontal cortex
VS	Vegetative state

Chapter One: Introduction

Self-Referential Processing

Since William James' conceptualization of the self as a multidimensional construct (James, 1890), the concept of self and all its constituents, has continued to be an important focus of study by philosophers and psychologists. Recently, the ability to experience stimuli related to the self-referential processing (SRP), has been ambitiously studied by cognitive neuroscientists. To study SRP sufficiently it is helpful to draw from phenomenology to produce an operational definition that would distinguish the "pre-reflective" (Zahavi, 2006) or "minimal self" (Gallagher, 2000) from the "reflective" (Zahavi, 2006) or "narrative self" (Gallagher, 2000). The pre-reflective self can be defined as the non-observational, immediate, pre-linguistic sense of "what is it like" to have an experience (e.g. the taste chocolate) whereas the reflective self can be defined as the explicit, conceptual awareness that the experience happened "to me" at some point in time (e.g. remembering what chocolate tastes like). These domains are considered to be interdependent in that the pre-reflective provides the features on which the reflective attends. Mishara (2007) warns that operationalizing the pre-reflective for scientific study is problematic because there is no way to rule out that reflection itself hasn't added some quality to the pre-reflective content. However, this reasonable warning may be unnecessary if one considers SRP to be slightly *more* conscious than the pre-reflective, but still lacking the explicit, "veridical processing" and "objective reasoning" characteristic of reflection (Northoff et al., 2006). In this case, SRP could be considered a basic "experiential self"-one that simply attributes the ownership of the phenomenal experience to the person.

Not surprisingly the above account of SRP captures a multitude of interoceptive/ exteroceptive and corporeal/representational domains of human experience. The domains that have been successfully adapted to neuroimaging methods consist of basic measures of our sense of self: self-awareness of one's own mental state, first-person perspective, autobiographical memory, sense of agency, and self-concept (Gillihan & Farah, 2005). A recent meta-analyses of neuroimaging studies of SRP that compared self-related to non-self-related stimuli across cognitive (imagination) and sensory stimuli (visual & auditory) modalities included tasks that involved trait adjectives, one's own name, self-face recognition, memory, emotions, and movements (Northoff et al., 2006). The authors determined that there is a core set of neuroanatomic regions active in all these paradigms called the cortical midline structures (CMS). These structures include the medial orbital prefrontal cortex (MOPFC), the ventromedial prefrontal cortex (VMPFC), the sub/pre- and supragenual anterior cingulate cortex (PACC, SACC), the dorsomedial prefrontal cortex (DMPFC), the medial parietal cortex (MPC), the posterior cingulate cortex (PCC), and the retrosplenial cortex (RSC; See Figure 1). These results suggest that the CMS are involved with SRP regardless of the cognitive or sensory modality conducted in the study.

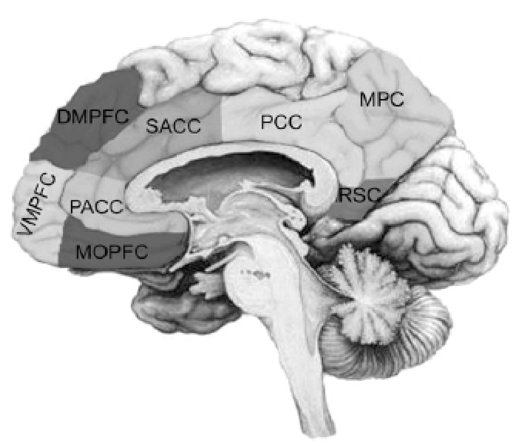

Figure 1. Cortical Midline Structures (Northoff et al., 2006)

Damasio (1999) constructed a tripartite hierarchy based on neurological findings of the relationship between cortical specialization and the self: the "proto-self," "core-self," and "autobiographical-self." The proto-self, which corresponds to the "pre-reflective," involves sensory cortical regions of the CMS and thus represents the most basic corporeal/sensory level of the self. In contrast, the autobiographical-self, which corresponds to the "reflective," includes higher executive processing regions of the CMS, and represents the autobiographical/verbal level of the self. Therefore, the core-self may correspond to the totality of the CMS and through SRP act as a bridge between lower and higher levels of self-referential stimuli. In conclusion, SRP and its neuroanatomic relationship with the CMS, makes for an important and useful construct to investigate when conducting research on the neural underpinnings of a sustained sense of self.

Disorders of Consciousness

While there is no current consensus on what defines human consciousness, two basic elements that aid in coming to an operational definition that can be used in the clinical setting include *arousal* (e.g. the behavioral continuum between sleep and wakefulness) and *awareness of environment and of self* (e.g. voluntary perceptional awareness of the environment; James, 1890; Plum & Posner, 2007; Laureys, Perrin, & Brédart, 2007). In accordance with researchers on disorders of consciousness (DOC), consciousness can be further operationalized for clinical purposes, as that which is observed upon bedside evaluation (Laureys et al. 2007). DOC typically result from an acute brain insult caused by hypoxic-ischemic neural degradation, traumatic brain injury, stroke, cardiac arrest, and the final stages of neurodegenerative diseases (Bekinschtein & Manes, 2008). DOC consists of three general states: the comatose state (Jennet

& Plum, 1972), the vegetative state (Multi-Society Task Force on PVS, 1994), and the minimally conscious state (Giacino & Kalmar, 2005).

Coma is described as a state of almost complete unresponsiveness in which the patient's eyes remain closed, display limited reflexes, no sleep cycle, and no signs of awareness. The typical duration of a coma is 2 weeks, however chronic cases are reported.

The *vegetative state* (VS) may develop from a comatose state and involves a complete absence of consciousness (as defined above) but *with* a preserved sleep cycle, autonomic function, and brain wave activity (thus differentiated from brain death). The patient may produce simple reflexes and nonvolitional activity. After 1 month the patient is considered to be in a *persistent* vegetative state (PVS) and if there is no chance of recovery they are considered be in a *permanent* VS.

A *minimally conscious state* (MCS) may develop from a partial recovery from VS in which consciousness awareness is observed but with severe cognitive and motor impairment. Certain nonreflexive behaviors occur, but are often inconsistently reproducible. Sometimes facial expressions are produced but again are inconsistent in response to simple commands. The following flow chart (see Figure 2) outlines the typical progression of the stages of DOC.

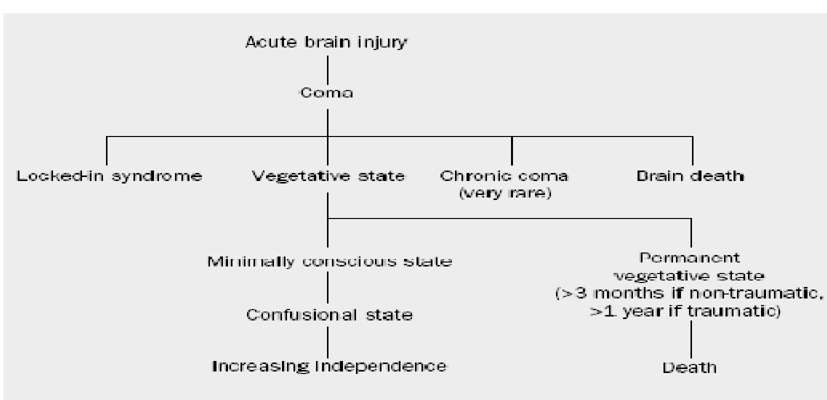

Figure 2. Progressive stages of DOC (Laureys, Owen, & Schiff, 2004).

Lastly, a peculiar condition called *locked-in syndrome*, is not a DOC but is often considered a related condition as it is characterized by complete paralysis of voluntary muscles throughout the body except for the eye muscles. These patients are fully conscious, but are unable to communicate through speech (Katz, Haig, Clark, & Dipaola, 1992). Typically, locked-in patients sustain damage to the ventral pons or mid-brain where motor pathways from the brain to the skeletal muscles are located (Damasio, 1999). Even more peculiar is the observation that even though locked-in patients experience the same range of emotions as before the injury, they typically do not report the horrifying terror and anguish one would expect.

The graph below (see Figure 3) conveniently illustrates the relationship between arousal and awareness and their contribution to DOC and normal physiological states (underlined). As described above, the comatose state is characterized by the least amount of arousal and awareness. Oddly, VS represents a dissociation between arousal and awareness where wakefulness remains intact without voluntary behavior or awareness. MCS displays similar levels of arousal as VS, but with more observable awareness (albeit inconsistent) of environmental stimuli.

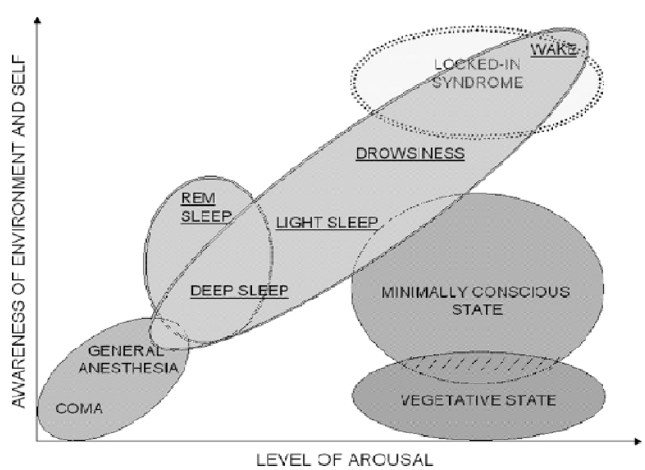

Figure 3. Awareness and Arousal in DOC (Laureys, Perrin, & Brédart, 2007)

Detecting Awareness in DOC

Detecting awareness in DOC with functional neuroimaging methods is a challenging endeavor given the difficulty in determining whether or not specific brain activity associated with a psychological task involves some level of conscious awareness or is likened to automatic activity (Greenberg, 2007). Simple bedside behavioral and neurological observations in the manner of "just asking" the patient can confirm conscious awareness when the patient responds "Yes I read the word awareness on this page." However, this approach is limited with more specific questions regarding inner mental functioning, particularly in more severe cases of DOC (Naccache, 2006).

The problem of determining conscious processing in DOC parallels what has become known as the Turing test in artificial intelligence (Turing, 1950; Stins, 2008). Alan Turing proposed that based on a number of questions-and-answers with a human interrogator, a machine would pass the Turing test if the human thought s/he was conversing with a human being. The focal issue of the Turing test is the aspect of communication-whether or not something shares our level of consciousness requires some mode of conversation that resembles our level of responding. Searle (1980) challenges the Turing test by proposing a thought experiment called the Chinese room argument. The thought experiment supposes that a computer programmed to process and respond to Chinese characters may pass the Turing test if it convinces a human Chinese speaker that it is in indeed a human Chinese speaker. However, Searle posits that if he were in a room hidden from the human Chinese speaker and was given a book containing instructions similar to the computer on how to translate the Chinese characters and then respond in Chinese accordingly, then given the fact that the Chinese characters are meaningless to him, he is in the same position as the computer-both he and the computer can follow instructions, but do not have an understanding of the meaning of the characters. Therefore, Searle concludes computers do not have minds.

In the study of DOC, Searle implies that we are unable to have direct access to the patient's subjective, first-person perspective and therefore it will always be uncertain if a rich mental life exists behind the patient's observable behavior (Stins, 2008). This assumption has been challenged by Owen et al. (2006) in which they conducted a fMRI scan of a woman diagnosed with VS (completely unresponsive) who was instructed to "imagine playing tennis" and "imagine walking through your house" and to maintain this for the duration of 30 seconds. The brain activity (supplementary motor area) and temporal sequence associated with these two instructions were indistinguishable from healthy controls subjects. Owen et al. concluded that not only did the patient understand the commands, but acted decisively and with intention. Greenberg (2007) and Nachev and Husain (2007) alternatively suggested that we cannot rule-out that the brain activity wasn't automatically triggered. Owen et al. (2007b) responded by running additional fMRI scans with control subjects who were instructed to just imagine the isolated words "tennis" and "house." These instructions did not elicit motor-related brain activity and therefore in Owen et al.'s opinion, substantiated their earlier conclusion. Since changes in behavior result from specific changes in brain activity, Owen et al.'s conclusion implies that the observed changes in brain activity associated with the initial instructions, *was* the behavior in that the patient exhibited an understanding and willingness to follow the instructions via the modulation of her brain activity (Stins, 2008).

Owen's group recently advanced this fMRI paradigm with a minimally conscious patient who was unable to functionally communicate at bedside by showing that this patient could communicate yes-or-no answers to simple questions (Monti et al., 2010). The technique involved having both healthy subjects and the patient first undergo a "localizer" scan that included a motor imagery task (e.g. "hit the ball on a tennis court") and a spatial imagery task (e.g. "imagine walking from room to room in your house"). This was then followed by a "communication" scan in which the subjects assigned "yes" or "no" to either imagery task and then applied the corresponding imagery task to answer simple autobiographical questions (e.g. "Do you have any brothers?"). Across all subjects, contrasts between the motor and spatial imagery task showed activation of the supplementary motor cortex and the parahippocampal gyrus, respectively. During the communication scan, the patient was observed to provide factually correct responses by consistently activating the brain regions that corresponded to either "yes" or "no." This study provides further evidence in support of Owen's conclusion that some DOC patient who are unable to communicate at bedside may have the ability to communicate by modulating brain activity.

Functional neuroimaging with DOC is a convenient method to measure covert neurophysiological changes associated with external stimuli without the need of overt behavioral responses. Robust activation patterns associated with the passive presentation of external stimuli have been observed in case studies involving PVS patients. de Jong, Willemsen, and Paans (1997) employed $H_2{}^{15}O$ PET while presenting an auditory story read by the patient's mother compared to nonword sounds. They observed activation in the ACC and temporal cortex during the mother's speech which was concluded to reflect emotional processing. In a similar PET study, Menon et al. (1998) found increased activation of the fusiform face area when faces of family members or close friends were presented to a PVS patient. It turns out that both of these patients did not meet an unequivocal diagnosis for PVS, and thus these results should be interpreted with caution.

In a more recent case study, Owen et al. (2007) conducted two combined PET/fMRI scans nine months apart with a PVS patient. The PET scan involved an auditory intelligibility task (declarative English sentences vs. distorted speech) and the fMRI scan involved a semantic ambiguity task (sentences with homonyms: "bark" & homophones: "knight/night" vs. low ambiguity sentences). At both time points the PET scan task showed expected activation of the left superior and middle temporal gyri and the fMRI scan task showed expected activation of the posterior inferior temporal lobe but not the superior inferior temporal lobe observed in healthy control subjects. These results suggest persistent and robust activation of the dominant language comprehension and discrimination areas across time. Again, the issue of ruling-out "comprehension" from automatic processing remains unclear.

Studies with larger samples of patients meeting full-criteria for PVS typically exhibit activation patterns that are distinguished from healthy controls. In a PET study of 15 PVS patients, noxious stimuli to the median nerve at the wrist, resulted in expected activation (although cerebral volume was 40% less than controls) of the mid-brain, contralateral thalamus, and primary somatosensory cortex in every patient (Laureys et al., 2002). However, controls also showed activation in the secondary somatosensory, bilateral insular, posterior parietal, and ACC cortices which suggest a disconnection between the primary somatosensory and higher-order association cortices. Likewise, a recent event-related fMRI study compared activation patterns associated with hearing one's own spoken name by a familiar voice between PVS (n = 7) and MCS (n = 4) patients (Di et al., 2007). Two of the PVS patients failed to show any activation. Three PVS patients showed activation of the primary auditory cortex. And two VS and four MCS patients showed higher-order associative temporal cortex activation in addition to the primary auditory cortex. The authors concluded that this paradigm may be a useful method in the preclinical differential diagnosis and subcategorization of MCS and PVS.

Recently, it has been suggested that employing a hierarchical approach to functional neuroimaging studies of DOC would better determine the degree and extent of preserved cognitive functioning in DOC (Owen et al., 2004; Laureys, Owen, & Schiff, 2004). This paradigm would progress from the simplest form of sensory processing to more complex forms of processing upon successful activation at each stage of complexity (Owen & Coleman, 2008). The hierarchical approach could involve the following progression from low to high cognitive complexity: sound perception → speech specific sound perception → comprehension via comparing ambiguous to unambiguous words → volition via sustained, word-specific imagery. Coleman and colleagues (2007) recently applied this hierarchical approach to a heterogeneous group of DOC patients (2 severely disabled, 5 MCS, & 7 PVS). The hierarchical paradigm involved auditory stimuli at the following levels: sound perception (intelligible speech and unintelligible noise vs. silent baseline) → speech specific sound perception (intelligible speech vs. unintelligible speech) → and finally, language comprehension (sentences with ambiguous words such as bark or knight/night vs. sentences without ambiguous words). The authors observed retained activation in the expected language processing areas of the left superior and inferior temporal cortices in the two severely disabled patients across all levels. Three PVS and two MCS patients showed similar activation in these language areas through the second level but showed marginally significant and case-specific variability at the third level of language processing. Four PVS and three MCS patients showed no activation at any of the levels of language processing.

In a follow-up study (Davis et al., 2007), these authors adapted the hierarchical approach to healthy subjects at progressive levels of awareness (awake, lightly sedated, deeply sedated) via administration of Propofol ($GABA_A$ potentiating compound used for sedation and anesthesia). The fMRI task involved the final stage (comprehension) of their previous study, and found bilateral temporal activation related to speech vs. silence across all levels of sedation. However, there was an absence of activation beginning at light sedation when distinguishing ambiguous vs. unambiguous sentences. Further, they found a decline in post-scan recognition memory for the sentences at light and deep levels of sedation. Thus, speech perception is intact throughout all levels of sedation, but speech comprehension declines at low levels of sedation.

Owen and Coleman (2008) warn that interpretation of the above findings must be approached with extreme caution since we cannot conclude that a DOC patient has "awareness" if they exhibit similar brain activation patterns as healthy subjects under deep sedation. Conversely, the possibility exists that if a DOC patient does exhibit similar brain activation patterns as healthy subjects who are fully awake, then we may conclude that the patient does indeed display conscious awareness. As a reminder, all of these possibilities are considered speculative given the problem of automatic activation. Although, the studies conducted by Owen et al. (2006, 2007b) and Monti et al. (2010) may be the first to address this problem.

Self-Referential Processing in DOC

Currently, there is a paucity of studies investigating functional brain activation patterns associated with self-referential processing (SRP) in DOC. As reported above, Di et al. (2007) observed activation of the higher-order association temporal cortex in MCS and PVS patients when hearing their own name spoken by a familiar voice. However, the authors did not specify whether or not systems involved with SRP were activated in these higher-order activation patterns. Staffen, Kronbichler, Aichhorn, Mair, and Ladurner (2006) investigated this question with a PVS patient and controls subjects who underwent an event-related fMRI scan while listening to unfamiliar persons speak his name versus another's name (e.g. "Martin, hello Martin). The authors observed bilateral activation in the medial prefrontal cortex (MPFC) in response to the patient's own name. Control subjects showed higher activition in the MPFC to their own name which was restricted to the left hemisphere. Both groups showed activation in language processing areas of the temporal lobe. The authors caution that since recognition of one's own name is a salient stimulus it may be a basic form of language processing that could exist independently from higher association areas that are typically disconnected in DOC. Consistent with this study, Laureys et al. (2004) conducted a PET study involving presentation of one's own name with an MCS patient who displayed inconsistent eye tracking, vocalizations, and orientation to new sounds. The authors observed widespread activation involving the precuneus, ACC, right temporoparietal lobes, left dorsal PFC, and bilateral angular gyri. Results from these two studies are consistent with functional neuroimaging studies employing this paradigm to investigate SRP in healthy subjects (Northoff et al., 2006).

Qin et al. (2010) is currently the only study that has investigated the relationship between brain regions involved in SRP and the presence of self in DOC. The study first conducted a series of localizer fMRI scans with healthy controls to determine regions of interest (ROI) that showed the strongest activation when hearing the subject's own name spoken by a familiar voice (SON-FV). The regions included the caudal ACC, anterior ACC, and the SMA, and were then applied as predetermined regions of interests during a fMRI block design with 7 VS and 4 MCS. Presentation of the SON-FV showed expected signal changes in these regions in all but one of the subjects. Separate post-hoc whole brain analyses that no longer relied on the ROIs confirmed these results and also showed activation of anterior and posterior regions of the cortical midline structures (CMS). Furthermore, they also showed a significant positive correlation between the amount of signal change in the caudal ACC and degree of consciousness. While this study does not address the neural mechanism of DOC (e.g. automatic activation), it does highlight the potential of applying SRP stimuli as a diagnostic marker of disordered consciousness.

In addition to fMRI and PET, recording of event-related potentials (ERP) is a promising electroencephalographic (EEG) method to detect residual SRP in DOC due its high temporal resolution and convenience of its application at the patient's bedside. Typically ERP studies use the P300 wave as an indicator of a shift in attention to deviant (or novel) stimuli immersed within the sequence of multiple occurrences of a stimulus (termed an "oddball paradigm"). Though a low percentage of P300 responses during passive auditory tasks are observed in healthy subjects (O'Mahony, Rowan, Walsh, & Coakley, 1990), the P300 has been evoked through conditioning techniques in comatose patients (Signorino, Acunto, Angeleri, & Pietropaoli, 1995).

Perrin and colleagues (2006) applied the oddball paradigm to study recognition of SON (deviant stimulus) in LIS, MCS, and VS patients. The authors observed evoked P300 in all LIS and MCS patients and in 3 of 5 VS patients. Further, the P300 latency was delayed in the VS and MCS patients compared to healthy control subjects. In a recent prospective study using the mismatch negativity (MMN) potential (analog of P300) the researchers found a significant correlation between the presence of MMN to SON and recovery from coma/VS to MCS (Qin et al., 2008). These studies highlight the utility of ERP methodology as a potential diagnostic and prognostic tool, however, since the P300 is also evoked during unconscious priming paradigms it is still unclear if it represents a type of preserved attentional mechanism in DOC (Laureys, Perrin, Brédart, 2007). Most importantly, these ERP studies converge with the above fMRI and PET studies in showing a distinctive response to self-referential stimuli in DOC.

The above studies highlight the opportunity to examine neural activity that is not overtly discernable through standard bedside neurological evaluation. Continued research has the potential to develop guidelines for clinical decision making as well as determine prognostic indicators for rehabilitative protocols designed around a patient's cognitive strengths. In addition, if the research by Owen et al. (2006, 2007b) and Monti et al. (2010) are substantiated across more subjects, then these paradigms may also be applied to clinical questions that address quality of life (e.g. pain; express thoughts; control aspects of their environment). Lastly, an anecdotal report by Coleman et al. (2007) highlights the positive impact these measures can have on the negative outlook experienced by family members and rehabilitative staff when intact functional activity is observed.

Though the above functional neuroimaging studies show promise in the study of DOC, a number of methodological issues should be considered. As highlighted throughout these sections, the most salient methodological issue is whether or not functional activation in response to passively directed external stimuli represents some level of phenomenal conscious awareness or is simply, familiar automatic activity (but see Owen et al, 2006, 2007b; Monti et al. 2010). Further, even if one concludes the latter, it is still unclear what type of automatic activity is observed. For example, since SON is a highly evocative stimuli typically encountered since infancy, it is unclear to what degree familiarity, emotional valence (positive or negative), or level of emotion arousal of SON evokes a shift in attention (Laureys, Perrin, Brédart, 2007). It all may depend on unexpectedness since the disrupting effect seems to disappear upon increased number of repetitions of SON. Though more research is required to determine the special status of SON, a justifiable conclusion is that even a momentary shift in attention to SON implies some degree of capacity to attend to evocative stimuli.

fMRI and PET in the study of DOC are methodologically complex across data acquisition, analysis, and interpretation (Laureys, Owen, & Schiff, 2004). In both PET and fMRI, parameters for data acquisition are informed by predetermined, often stable values of brain metabolism in healthy subjects. Since DOC patients are typically characterized by abnormal brain metabolism, determining the parameters for glucose transport, oxygen use, and local hemodynamics remains elusive. Specific to fMRI studies, fitting functional imaging data to structural imaging data and normalizing this data in reference to normal brain parameters will be challenging in DOC patients with sustained diffuse cerebral pathology or focal lesions. In addition, attention to the functional capacity of the patient (e.g. a patient with abnormal brainstem auditory evoked responses would be better studied via a visual task) and cognitive capacity (e.g. a balance between complexity and overload) must be considered when designing the experiment. Given these methodological issues, functional neuroimaging should be considered a complementary technique to the already standardized and established guidelines in the assessment and conceptualization of awareness in DOC.

Study Rational and Aim

The above functional neuroimaging studies involving fMRI, PET, and EEG have consistently shown residual brain activation in response to a variety of auditory, visual, tactile, and imaginary stimuli in patients with a diagnosis of disordered consciousness. These studies evidence differential brain activation patterns that are comparable to healthy controls and distinguishable between diagnostic categories within the DOC spectrum, thus supporting the possibility of applying functional neuroimaging as a method to identify diagnostic and prognostic functional neuroanatomical markers (Di, Boly, Weng, Ledoux, & Laureys, 2008). The recent study by Qin et al. (2010) demonstrating a correlation between the degree of consciousness in patients with DOC and brain activity during self-related stimuli provide initial group-level evidence for the presence of a diagnostic marker in DOC. Evidence of patients showing volitional brain activity associated with imagining playing tennis and spatial navigation (Owen et al., 2006) and responding accurately to yes/no questions (Monti et al., 2010) imply that some functioning of awareness of self must be present to perform these tasks. Thus measuring brain activation associated to self-related stimuli (e.g. self-referential processing) has the potential to guide diagnosis as well as possibly broaden our understanding of a patient's preserved ability to engage in higher-level cognitive processing.

The aim of this study is to use fMRI to explore brain activity during the auditory presentation of two personally relevant language stimuli involved in self-referential processing (the patient's name and the patient's mother's voice) in a 7 year-old pediatric patient who sustained both a spinal cord injury and anoxic brain injury at 16 months of age, rendering her unable to communicate, quadriplegic, and ventilator dependent. Neurological evaluation of behavioral output (restricted to head and eye-movements only) indicated that the patient could produce sustained visual tracking of light and mirror stimuli, but could not produce responses to verbal or gestural commands. Since the behavioral evidence of awareness in this patient is minimal (and possibly spontaneous) and does not explicitly indicate purposeful behavior, the patient's level of awareness is still uncertain.

Chapter Two: Methods

Subject

The patient was recruited through the UT Medical Center Department of Neurology and evaluated by a neurologist (JHD). The pediatric patient in this study was 7 years-old and sustained a spinal injury and head trauma at approximately 16 months of age rendering her quadriplegic and ventilator dependent. Informed consent was received by both the patient's legal guardians (biological parents) and was approved by the University of Tennessee Institutional Review Board and University of Tennessee Graduate School of Medicine Institutional Review Board.

Assessment

The patient underwent an initial MRI of the brain following her injury. This indicated bilateral basal ganglia lesions from her hypoxic-ischemia injury that occurred at the scene of the accident. Recent MRI was unremarkable, showing a normal size ventricular system and sulci, normal brain stem and cerebellum, and no evidence of a mass lesion or mass effect. MRI of the spine demonstrated a post-traumatic cyst at the level of C1-C3 indicative of spinal injury. MRI of the thoracic and lumbar spine was normal. Recent auditory evoked potentials of the brainstem produced normal wave form amplitude, configuration, ratios, and latencies. No significant asymmetries were present. Consistent with quadriplegia, median nerve somatosensory evoked potentials at the wrist were severely abnormal. Overall, the patient's MRI and EEG tests are unremarkable and do not explain her severity of cognitive impairment.

As stated above, minimally conscious state (MCS) is identified as a condition of severely impaired consciousness with minimal but definite behavioral evidence of self or environmental awareness (Posner, Saper, Schiff, & Plum, 2007). The diagnosis for MCS is probable because the patient displays reproducible sustained visual tracking to light and mirror stimuli and does not follow simple verbal or gestural commands. However, a diagnosis of MCS and the exact quality of her cognitive functioning is still in question because the patient's quadriplegic status does not permit assessment of reproducible motor behavior, therefore restricting her neurological evaluation to head and eye-movements only.

Image data Acquisition and Analysis

An event-related fMRI was used to explore brain activity associated with hearing a phrase (e.g. "Allison, hello Allison"). The auditory name/voice stimuli were digitally recorded using Audacity software (Audacity Inc.) and were recorded from the patient's mother as the familiar voice and 5 women, none which were familiar to the patient and knew her real first name. The auditory stimuli included the subject's own name spoken by a familiar voice (SON-FV), SON spoken by unfamiliar voices (SON-UV), unknown name spoken by a FV (UN-FV), and UN-UV. The patient's mother selected unknown names based on her best estimation of the patient's lifetime encounter or familiarity with these names. Unknown names were matched to the gender and number of syllables of the subject's own name and unknown voices were matched to the regional accent (midwestern United States) of the patient's mother. Eight fMRI runs were conducted where each contained 25 repetitions of each auditory stimuli and 25 repetitions of fixed, silent null events (duration = 2000 ms, ISI = 1000 ms). The patient was awake with eyes open during the study and required artificial ventilation with a MRI-compatible ventilator. The auditory stimuli were presented through MRI-compatible noise-attenuating headphones. To minimize head motion during the scanning session, towels were placed around the patient's head within the head coil.

Imaging was performed on a 1.5 Siemen's MRI scanner with a standard head coil at the University of Tennessee Department of Radiology. Eight runs consisting of 150 whole-brain functional T2*-weighted echo planar images were acquired, each comprising 27 slices parallel to the intercommissural (AC-PC) line: slice thickness, 3 mm; repetition time (TR), 2500 ms; echo time (TE) 50 ms; flip angle 90 degrees; matrix, 64 x 64; field of view (FOV), 192 mm x 192 mm a. Prior to the functional scans, a whole-brain anatomical T2-Haste image was acquired for functional registration and localization: slice thickness, 3 mm; repetition time (TR), 1000 ms; echo time (TE) 86 ms; flip angle 90 degrees; matrix, 256 x 256; field of view (FOV), 192 mm x 192 mm.

Data preprocessing took place using Statistical Parametric Mapping (SPM8) method (Wellcome Department of Cognitive Neurology, London, United Kingdom). Each volume of the fMRI image series was aligned to the first functional with masking for removal of a signal artifact in left occipital region secondary to craniocervical fusion surgery. Then the high resolution T2*-Haste anatomical image was normalized to the functional images.

Following the above preprocessing, statistical parametric mapping was also performed on the SPM8 software. The four auditory stimuli (SON-FV, SON-UV, UN-FV, and UN-UV) were included as regressors along with six motion regressors (derived from the alignment step) within the general linear model. Contrasts were performed to determine differential brain activation between all auditory stimuli (AUD) versus implicit baseline, SON versus UN, and FV versus UF. Each contrast was examined using voxelwise t-tests. To deal with the problem of multiple comparisons, an uncorrected *p*-value of 0.001 was applied at each voxel. This was followed by retaining clusters with an corrected and/or uncorrected cluster size threshold of $p < 0.05$ at the whole brain level.

Chapter Three: Results

Blood-oxygen-level-dependent (BOLD) activations across all contrasts were regionally determined using a three dimensional brain atlas (Duvernoy, 1991) that provides MRI images in coronal, sagittal, and horizontal planes as well as photographs of matching brain slices. This method is considered superior to using an automated coordinate brain atlases based on a standardized brain as it requires use of macroanatomical landmarks specific to the individual anatomy (Devlin & Poldrak, 2007).

Only the first two functional runs (300 total volumes) were included in the GLM and subsequent analyses due to substantial head movement (> 3 mm) during the six remaining runs (see Figure 4). Collapsing across all auditory stimuli relative to baseline (AUD > Baseline) revealed activation of the anterior portion of the left transverse temporal gyrus (primary auditory cortex) extending into the ventral region of Wernicke's area and Heschl's gyrus (see Figure 5). No interaction effect was observed for SON-FV versus SON-UV or UN-FV versus UN-UN at a voxelwise threshold of $p < 0.001$ or $p < 0.005$. The following contrasts are main effects and are highlighted with their corresponding corrected and uncorrected cluster-level *p*-values and Brodmann area (BA) in Table 1. SON > UN contrast revealed activation in the right middle frontal gyrus in the dorsal lateral prefrontal region (DLPFC; see Figure 6) as well as in the left ventral region of the medial prefrontal cortex (vMPFC; see Figure 7). UN > SON contrast revealed a large region of activation in the middle temporal gyrus that extended into a small area of the middle occipital gyrus (see Figure 8). FV > UV revealed activation of the left supramarginal gyrus that includes the post-central gyrus (see Figure 9). UV > FV revealed no clusters of activation at either $p < 0.001$ or $p < 0.005$.

Table 1.

Brain activation during auditory stimuli.

Brain areas	Side	Cluster size (mm^3)	*p*(corr)	*p*(uncorr)
AUD > Baseline				
Anterior Transverse Temporal Gyrus (BA 41/42)	L	24	0.021	0.001
SON > UN				
Middle Frontal Gyrus (DLPFC) (BA 9)	R	8	0.474	0.043
Ventromedial Prefrontal Cortex (BA 10)	L	7	0.568	0.056
UN > SON				
Middle Temporal Gyrus (BA 21)	R	29	0.009	0.001
FV > UV				
Anterior Supramarginal gyrus (BA 40)	L	21	0.037	0.002

$p = 0.001$
BA = Brodmann Area

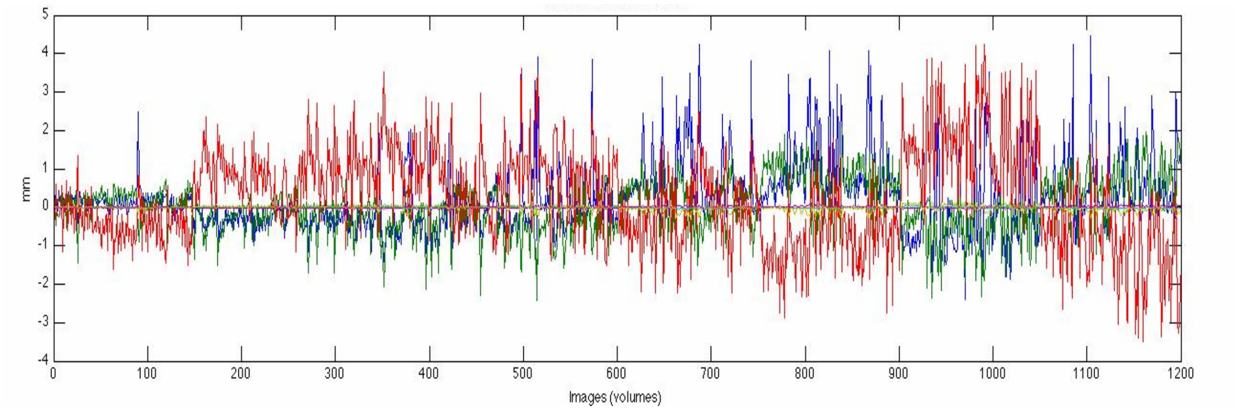

Figure 4. Head motion across 8 functional runs (150 volumes each).

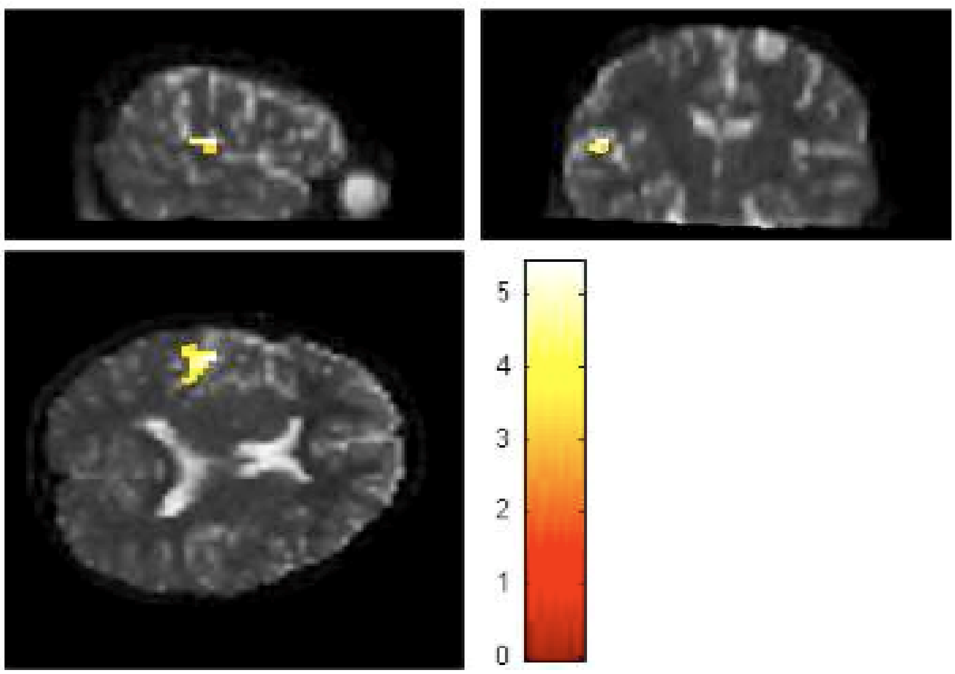

Figure 5. Activation of the left anterior transverse temporal gyrus (AUD > baseline).

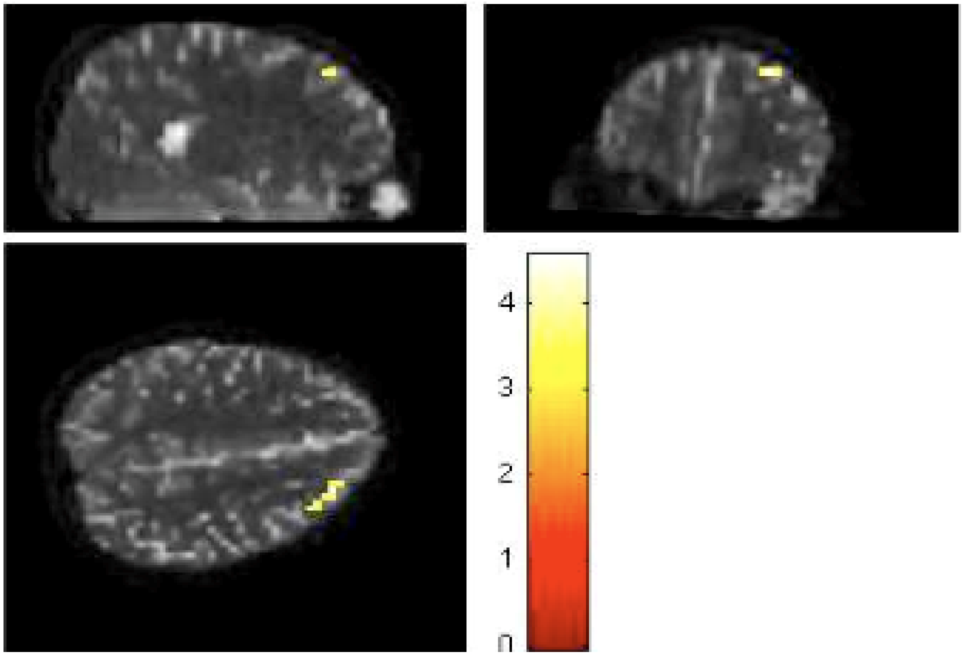

Figure 6. Activation of the right middle frontal gyrus (SON > UN).

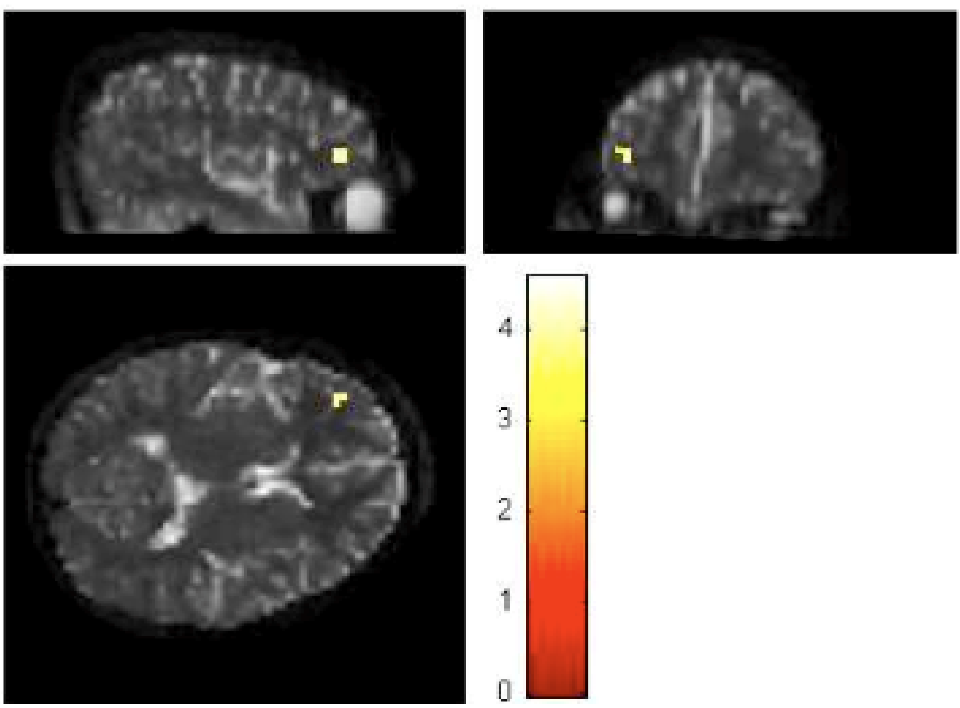

Figure 7. Activation of the left ventromedial prefrontal cortex (SON > UN).

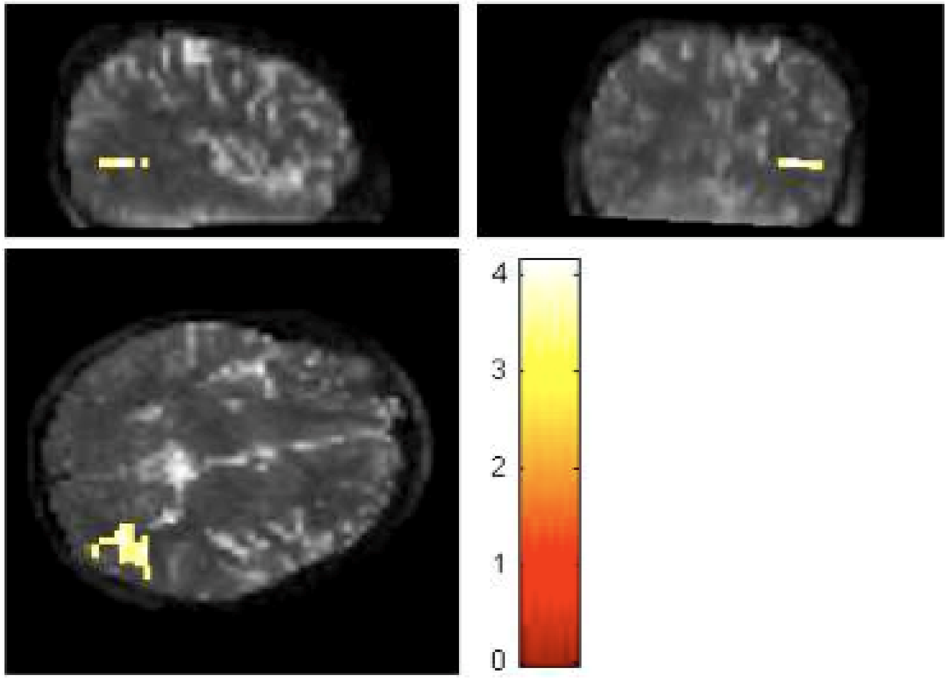

Figure 8. Activation of the right middle temporal gyrus (UN > SON).

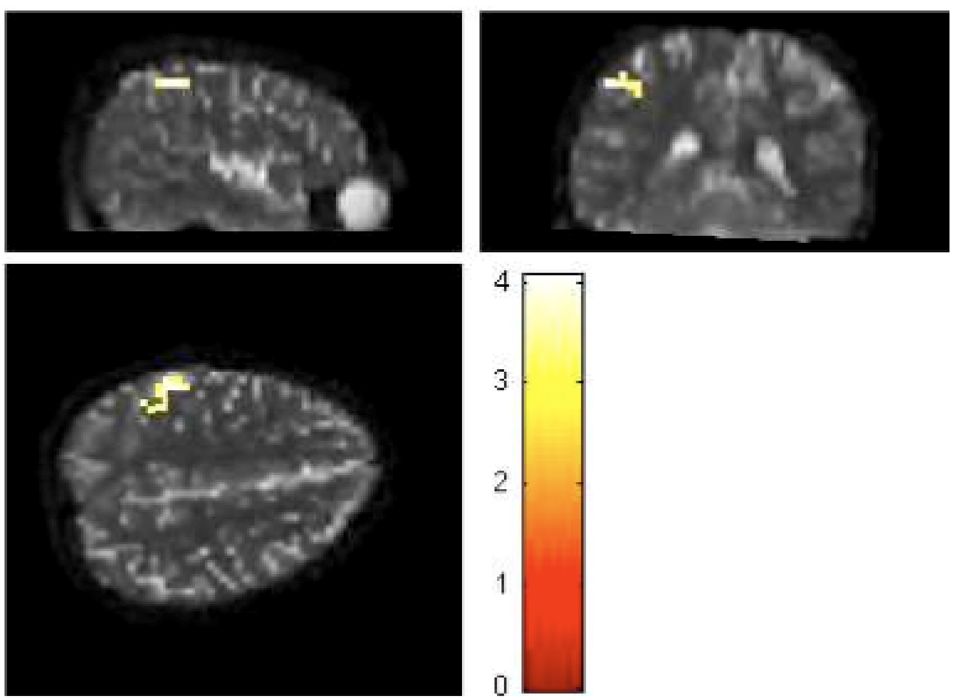

Figure 9. Activation of the left supramarginal gyrus (FV > UV).

Chapter Four: Discussion

The patient in this study was 16 months-old when she sustained a spinal injury and anoxic brain injury rendering her unable to communicate, quadriplegic, and ventilator dependent. Prior to the patient's injuries, she was reported to meet normal developmental milestones related to the tasks examined in this study, in that she was able to attend to her own name, her mother's voice, and could speak single-words productively and understand simple commands (Hollich & Houston, 2007).

The patient was 7 years-old at the time of the study. Her clinical presentation restricted our behavioral neurological evaluation to head and eye-movements only, thus limiting our ability to complete a full behavioral neurological exam and determine this patient's level of awareness of self and her environment. In addition, a structural MRI prior to her inclusion in this study was unremarkable and did not show volumetric abnormalities in brain regions implicated in the maturation of the ability to represent the self (Lewis & Carmody, 2008).

The aim of this study was to use functional neuroimaging to identify and measure brain activity during a self-referential auditory processing task involving personally relevant language stimuli (SON-FV, SON-UV, UN-FV, and UN-UV). Collapsing across all auditory stimuli, AUD > baseline revealed a substantial region of activation in the anterior portion of the left transverse temporal gyrus (primary auditory cortex) spreading into ventral region of Wernicke's area and Heschle's gyrus. This finding is consistent with PET studies showing activation of the primary auditory cortex to simple auditory stimuli (e.g. clicks) in both healthy controls and DOC patients (Laureys et al. 2000, Boly et al. 2004). The left lateralization of this area is consistently observed across healthy adults and children during language processing tasks (Binder et al., 1995; Ahmad et al., 2003).

Contrasts between SON versus UN (uncorrected $p < 0.001$) revealed activation of the anterior portion of the right dorsolateral prefrontal cortex (DLPFC) within the right middle frontal gyrus and activation of the left ventral medial prefrontal cortex (VMPFC) during presentation of the SON. Activation of the DLPFC is consistent with Carmody and Lewis (2006) who observed activation in the middle frontal cortex, middle temporal and superior temporal cortex, and cuneus in healthy young adults during this paradigm. In addition, activation of the DLPFC has also been observed in healthy subjects involved in making evaluations about the self (Fossati et al., 2003, Schmitz, Kawahara-Baccus, & Sterling, 2004). Activation of the vMPFC is comparable to studies demonstrating responses in the dorsal regions of the medial prefrontal cortex (MPFC) when hearing SON versus UN name in DOC patients and in healthy controls (Laureys et al., 2004; Staffen et al. 2006). vMPFC is considered a constituent of the cortical midline structures (CMS) and together are proposed to play a key role in self-referential processing across a variety of tasks (Northoff & Bermpohl, 2004; Northoff et al., 2006).

Activation of the right middle temporal gyrus (MTG) was observed during the presentation of the UN versus SON (uncorrected $p < 0.001$). Studies comparing brain activation between SON versus UN have not reported activation associated with UN, making it difficult to directly compare this finding. While a detailed role of the MTG is still emerging, left lateralized activation of this region has been observed in 5-7 year-old children when listening to short stories (Ahmad, Balsamo, Sachs, Xu, & Gaillard, 2003). In addition, Balsamo et al. (2002) observed bilateral activation (but greater left activation) in 7-9 year-old children during an auditory naming task. Therefore activation of the MTG in this patient may reflect a nonspecific recognition of language when hearing an UN.

Lastly, the contrast between FV versus UV activated a large region of the anterior supramarginal gyrus (SMG) during presentation of FV and did not reveal any significant activation for UV. Activation of the SMG has not been observed in neuroimaging studies investigating voice familiarity. Bekinschtein et al. (2004) observed a strong pattern of activation in the right amygdala, insula, and inferior frontal regions and weaker activation in auditory processing regions of the left temporal lobe in adult MCS patient (uncorrected $p < 0.001$). Consistent with this latter finding, Machado (2008) studied an 8 year-old PVS patient and found a significant lateralized ERP response in the left anterior/posterior temporal regions and also no response to the UV.

The SMG, mainly the ventral region, is associated with a wide variety of language processes involved in speech production, semantic recognition, and the sound of a word (Price, 2010). Consistent with these processes, the SMG is connected to auditory processing regions of the posterior supratemporal cortex and a portion of the inferior frontal gyrus (Catani, Jones, & ffytche, 2005). While speculative, this may implicate the SMG as a higher association area involved in auditory processing of speech. This account may explain the lack of activation observed during presentation of UV as there was possibly no orienting/attentional response and therefore no higher-level associative processing. In addition, neural activity during associative processing may simply be greater than activity associated with learning a new stimulus (e.g. unfamiliar voice; Birkett et al. 2002).

Taken together, these results are consistent with the literature indicating at the very least preserved brain activation during the presentation of auditory language as evidenced by a robust activation in the left primary auditory cortex across all stimuli. Activation of the vMPFC and DLPFC during the SON also suggests preserved brain activation involved in processing self-related stimuli. As already stated, the vMPFC is a component of the CMS which have been consistently implicated in self-referential processing (Northoff & Bermpohl, 2004; Northoff et al., 2006). A recent meta-analysis of fMRI and PET studies involving self-reflection tasks supports the role of the vMPFC in processing self-referential stimuli versus other-referential stimuli (van der Meer, Costafreda, Aleman, & David, 2010). This analysis also specifies the role of the vMPFC as being involved in the affective processing of self-related information. Northoff and Bermpohl (2004) and Northoff et al. (2006) suggest that there is an emotional component to self-referential processing as there is a positive relationship between the relevance to the self and vMPFC activation. This relationship is consistent with Gusnard et al. (2001) who have found the vMPFC to be involved with assessing the salience of a stimulus. Anatomically, the vMPFC shares interconnections with the limbic system (Ongur and Price, 2000) and plays an important role in emotional processing and regulation (Simpson et al., 2000). The DLPFC is also implicated (van der Meer et al., 2010) as it exerts executive control over the vMPFC and as stated above is involved in making evaluations of the self (Fossati et al., 2003, Schmitz, Kawahara-Baccus, & Sterling, 2004). Activation of these areas in this study therefore suggests the existence of a preserved network involved in attending and evaluating affective information that is inherent to hearing one's own name. This would then support the lack of activation of these prefrontal regions when hearing an UN as this stimulus likely holds minimal affective salience and is rather processed as neutral language stimuli within the left MTG.

There are some important limitations of this study. First, because direct behavioral measurement of self versus other awareness cannot not be measured in this patient, the level of conscious processing of these stimuli is still unknown. As stated above, studies in PVS and MCS patients as well as sedated subjects have shown similar activation patterns during auditory processing. In addition, the finding that activation of vMPFC and other CMS regions are observed during passive resting state conditions suggests that these regions are also involved in more implicit processing of self-related information. A second limitation is that activation associated to the SON and the FV may not be a preserved response to self-relevant stimuli, but rather a more basic response to exceedingly familiar stimuli. Future studies investigating the *degree* of familiarity by comparing brain activation across historically familiar stimuli, recently conditioned stimuli, and unfamiliar stimuli may help discern if brain activity associated with self-relevant stimuli show differential patterns. A third limitation concerns the patient's cognitive capacity to actually represent the self and other. Although there was no evidence of volumetric abnormalities in brain regions implicated in the ability to represent the self and others (Lewis & Carmody, 2008), it is possible that her injuries at 16 months of age affected her natural course of cognitive development. More specifically, her brain injury may have disrupted the transactional relationship (Fox, Calkins, & Bell, 1994) between the natural course of brain maturation and exposure to enriching environmental factors that together contribute to the development of basic cognitive representational abilities typically observed in 7 year-old children (e.g. meta-cognition, self-recognition, personal pronoun use, self-conscious emotions, imitation, theory of mind; Slater & Lewis, 2007). Thus it remains unclear if her brain activation patterns should be considered in terms of the standard expected development based on her chronological age or considered in terms of an earlier developmental time point. Fourth, because the design was a single case limits generalization, particularly with studies that include contrasts with a healthy control sample. Including an age-matched healthy control sample could address questions regarding whether or not the patient's initial hypoxic brain injury and subsequent functional limitations contributed to difference in brain activation during these tasks and are representative of her chronological age. Lastly, there was substantial motion artifact that prevented three-quarters of the data from being included in the analyses. Though there was still a sufficient amount of data collected in the first two functional runs (total of 50 activation periods per stimuli; Huettel & McCarthy, 2001), the probability of detecting a significant effect across voxels (power) would have likely been enhanced if motion were absent. Employing a head restraint device (e.g. bite bar; thermoplastic mask) can minimize motion, however, these methods are often not feasible due to specific limitations of the patient population and financial/logistical constraints related to customizing these devices.

The results of this study support the application of fMRI as a method to gain valuable information on the presence of residual cognitive processes in pediatric patients within the spectrum of DOC. Although the data do not directly inform the differential diagnosis of this patient, the observation of preserved brain activation during auditory processing may warrant continued rehabilitative attempts as her functional anatomy at the very least is minimally intact.

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