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Identifying Electrophysiological Components of Covert Awareness in Patients with Disorders of Consciousness

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Abstract

Naturalistic stimuli evoke synchronous patterns of neural activity between individuals in sensory and higher cognitive, “executive” networks of the brain. fMRI paradigms developed to measure this inter-subject synchronization have been extended to test for executive processing in behaviourally non-responsive patients as a neural marker of awareness. This thesis adapted one such paradigm for use in EEG, a low-cost, portable neuroimaging technique that can be administered at a patient’s bedside. Healthy participants listened to a suspenseful auditory narrative during EEG recording. Significant inter-subject synchronization was found throughout the audio but was significantly reduced during a scrambled control condition. This paradigm was then used to evaluate executive processing in a cohort of patients. One locked-in patient and one patient in a vegetative state were significantly synchronized to healthy controls during the audio. EEG is a suitable tool to detect executive processing, a proxy measure of awareness, in patients who are behaviourally non-responsive.

Keywords: Disorders of consciousness, Electroencephalography, Inter-subject neural synchronization, Naturalistic auditory stimuli, Correlated components analysis

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Chapter 1: Introduction

Arousal and Awareness

Uncovering the neural basis of consciousness is one of the most complex and fascinating puzzles facing modern neuroscience. While there is no fully agreed upon description of what consciousness is, or what role it plays in human behaviour, the clinical definition offers an intuitive and pragmatic characterization of its fundamental dimensions. This provides a tractable framework to study the function of consciousness, its supporting neural architecture, and, importantly, pathologies that affect it. Clinically, consciousness emerges at the nexus of two distinct but connected psychological dimensions: arousal and awareness (Zeman, 2001). The first dimension, arousal, is an index of wakefulness; a person is in a state of high arousal while they are awake and alert, and low arousal while they are asleep or under anaesthesia (Laureys, Owen, & Schiff, 2004). Wakefulness is maintained by the reticular formation of the brainstem and its projections to various thalamic structures and areas of the basal forebrain (Saper, Scammell, & Lu, 2005). Damage to any of these areas can disrupt sleep-wake function and lead to a clinical impairment in arousal (Laureys *et al*., 2004). Sleep and wakefulness are readily identifiable based on observable behaviour (i.e., eyes open or closed) but extensive electrophysiological research has established canonical markers of sleep which allow for valid, reliable measurement of these states (Owen, 2013).

The second dimension, awareness, encompasses the totality of cognitive, perceptual, and affective contents of experience (Posner, Saper, Schiff, & Plum, 2008). Broadly, awareness refers to a person’s experience of themselves and their surroundings. Unlike arousal, awareness cannot be measured directly; whereas some of its constituents can be assessed using carefully designed experiments (e.g., attention), indices of awareness rely entirely on verbal or behavioural responses to stimuli or the environment (i.e., responding to commands; Laureys *et al*., 2004). Recent clinical evidence suggests that the frontoparietal cortices and their connections to thalamic nuclei are crucial for the maintenance of awareness (Crone *et al*., 2014; Dehaene & Naccache, 2001; Fernandez-

Espejo, Rossit, & Owen, 2015). However, the neural mechanisms and functional dynamics involved in awareness have not been resolved (Laureys *et al*., 2004).

In healthy adults, arousal and awareness are highly correlated; awareness diminishes alongside arousal during dreamless sleep or when under anaesthesia, and returns upon waking (Laureys *et al*., 2004). Nevertheless, there are notable exceptions to this relationship. Dreams, for example, are occasionally accompanied by varying levels of awareness, whereas absence (petit mal) seizures do not affect arousal but result in a temporary focal disruption of awareness (Blumenfeld, 2005, 2012). Still, the most profound dissociations between arousal and awareness follow some instances of acute brain injury (Zeman, 2001). Severe traumatic (insult) and non-traumatic (organic) brain damage can lead to pathological impairments in awareness. Clinically, these conditions are referred to as disorders of consciousness (DOC). These include coma, the vegetative state, and the minimally conscious state. Each of these disorders has a distinct degree of separation from regular consciousness and, typically, reflect different phases of recovery following serious brain injury (Figure 1).

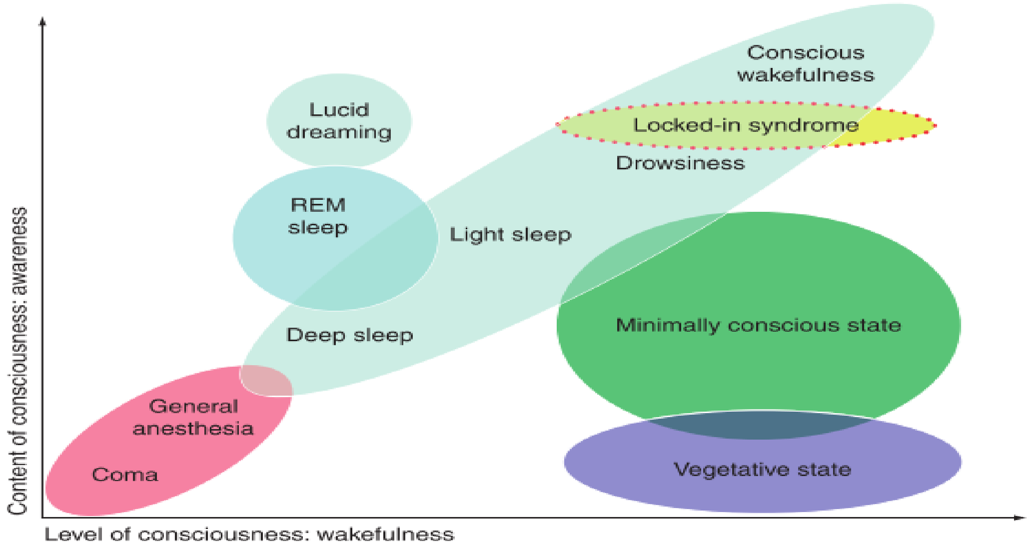

Figure 1. Conscious states at different levels of arousal and awareness (From Laureys *et al*., 2004).

Disorders of Consciousness

At the lowest point along the dimensions of wakefulness and awareness is the coma. Coma is a state of prolonged unconsciousness representing extensive brain dysfunction. Patients in a coma lack both awareness (behaviourally unresponsive) and, wakefulness (eyes remain closed), despite retaining most major brainstem function (Bernat, 2006; Laureys, Boly, Moonen, & Maquet, 2009). Electroencephalographic (EEG) recordings from coma patients are dominated by low frequency oscillations and the metabolic demands of the comatose brain are significantly reduced relative to healthy individuals (Laureys *et al*., 2004; Young, 2000). Typically, patients will emerge from a coma within 2-4 weeks post-injury. However, at this stage, clinical outcomes are highly variable; some go on to make a full or partial recovery, whereas a small number of patients who wake from a coma do not regain awareness (Laureys *et al*., 2009). These patients are diagnosed as being in a vegetative state.

The vegetative state is defined as a state of wakefulness without awareness (Andrews, Murphy, Munday, & Littlewood, 1996). Patients in a vegetative state exhibit eye-opening and closing behaviours that resemble circadian sleep-wake cycles but do not demonstrate any discernible evidence of awareness. During clinical assessment, they remain unresponsive to verbal command (e.g., “move your left hand”) and do not react to auditory, tactile, visual, or noxious stimuli (Gibson *et al*., 2014; Owen, 2008). Motor movements (e.g., head turning, eye movements, changing facial expressions) and vocalizations are routinely observed in patients who are in a vegetative state; however, they do not occur in response to stimulation, command, or environmental triggers and are not considered to reflect voluntary or purposeful behaviour (Andrews *et al*., 1996). Like coma, patients who are in a vegetative state have a characteristic slowing of EEG compared to healthy individuals and decreased neuronal metabolic activity, though not to the same extent (Kotchoubey *et al*., 2005; Laureys *et al*., 2004). The vegetative state is thought to result from diffuse cortical and thalamic damage, though the precise etiology is not well understood (Owen, 2008; Owen *et al*., 2006). The likelihood of making a full recovery from a vegetative state is low and diminishes over time (Owen, 2008). Some patients remain in a vegetative state indefinitely, with the diagnosis of a permanent vegetative state made six months after non-traumatic brain injury or after twelve months in cases of traumatic brain injury (Owen, 2008). However, this is not the fate of all patients diagnosed as being in a vegetative state. Indeed, some patients improve and regain some degree awareness. This return of awareness signifies a qualitative shift in a patient's conscious state and marks the progression from a vegetative state to a minimally conscious state.

Patients in a minimally conscious state demonstrate intermittent behavioural evidence of awareness (Giacino *et al*., 2002; Owen, 2008). Unlike patients in a vegetative state, patients in a minimally conscious state display non-reflexive, goal-directed behaviours in response to stimuli or verbal command (i.e., they demonstrate command-following). Their responses may be limited to simple actions such as moving one's hand when instructed, or encompass more sophisticated behaviours such as object manipulation or verbal/gestural communication (Laureys *et al*., 2009; Owen, 2008). The designations of minimally conscious state – minus (MCS-) and minimally conscious state – plus (MCS+) have recently been proposed to more accurately characterize a patient's level of recovered awareness and function. Patients categorized as MCS+ can produce gestural responses or verbalizations to one or more commands, whereas patients designated as MCS- produce only simple, but purposeful, behaviour (Bruno *et al*., 2012; Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011). The prognostic outcomes for patients who progress to a minimally conscious state are drastically improved compared to those in a vegetative state. The minimally conscious state is often a transitory period between coma or a vegetative state and recovery, though some patients do not progress beyond this state. Patients are considered to have emerged from a minimally conscious state if they can demonstrate consistent and reliable communication and exhibit functional discrimination between two or more objects (Giacino *et al*., 2002).

In rare cases, serious brain injury can result in complete paralysis while sparing arousal and awareness (Tart, 2001). This is a condition called locked in syndrome and, although it is not generally considered to be a DOC, it is frequently misdiagnosed as one. Locked-in syndrome is typically caused by a brainstem lesion (e.g., stroke), often involving the ventral pontine regions (Schiff, 2006). Diagnosing locked-in syndrome is exceptionally difficult because its acute stages closely resemble the clinical progression of the vegetative state. Patients may remain in a coma for weeks after injury and wake in a state of paralysis, rendering them unable to communicate or produce clear evidence of their awareness. Physiologically, some patients with locked-in syndrome retain partial control of their extremities (e.g., fingers, toes) but, most have preserved ability to direct their vertical eye movements. However, these can be extremely subtle behaviours which may be overlooked or dismissed during clinical examination. Consequently, it can take months or years before an accurate diagnosis is made (Laureys *et al*., 2005). Once awareness is established, however, eye movements often form the basis for a system of communication between the patients, their medical care team, and their families.

Diagnosing Disorders of Consciousness

Clinical assessments of awareness following severe brain injury are completed using standardized behavioural scales, such as the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) or the JKF Coma Recovery Scale - Revised (CSR-R; Kalmar & Giacino, 2005). The GCS is divided into three subscales of function (i.e., eye opening, verbal response, motor response) and is most often administered by first responders and emergency care specialists in cases of traumatic head injury (Bernat, 2006). Scores on the GCS range from 3 – 15, with low scores (e.g., < 9) representing moderate to severe dysfunction (Laureys, Perrin, & Brédart, 2007; Teasdale & Jennett, 1974). Although the GCS is frequently used as a rapid evaluation of state-awareness following severe trauma, it is not sensitive to subtle signs of awareness which require extended, careful examination to detect. Moreover, the GCS only measures a limited range of neurological functions, making it insufficient for diagnoses (Bernat, 2006). Once a patient’s condition has stabilized, the CRS-R should be used for further assessments.

The CRS-R is a behavioural neuropsychological test administered after a patient has recovered from a coma. It is divided into six subscales measuring visual, auditory, verbal, and motor function, as well as their level of arousal, and communication ability (Kalmar & Giacino, 2005). The subscales of the CRS-R are organized hierarchically: the first item in each scale tests reflexive function, whereas later items assess command-following and other cognitively mediated behaviours (Schnakers *et al*., 2009). Scores on the CRS-R can range from 0 – 23, with lower scores representing lower awareness or a lack thereof. In contrast to the GCS, the CRS-R provides suggested diagnostic criteria for the vegetative state, the minimally conscious state, and the emergence from a minimally conscious state based on a patient’s observed level of function during examination

(Schnakers *et al*., 2009). The CRS-R can be administered at numerous time points to track a patient's day-to-day awareness as well as their recovery over time, and this has been shown to predict, to some extent, patient outcomes (Giacino, Kezmarsky, DeLuca, & Cicerone, 1991; Pignat *et al*., 2016).

As it stands, behavioural assessment is the clinical "gold standard" to diagnose DOC (Giacino *et al*., 2009). However, behavioural measures of awareness are not sensitive to the perceptual, cognitive, and psychomotor dysfunctions that frequently result from serious brain injury, and cannot differentiate between these impairments and a genuine lack of awareness (Monti *et al*., 2010). Failure to respond to standardized tests like the CRS-R may be indicative of any number of neuropsychological impairments, including, but not limited to, those affecting awareness. Diagnoses made solely on the basis of behaviour may, therefore, capture these functional disabilities rather than provide an accurate appraisal of a patient's conscious state. Consequently, patients who are behaviourally unresponsive, but aware nonetheless (i.e., covertly aware), may be diagnosed as being in a vegetative state. Indeed, the rate of misdiagnosis in patients with DOC is estimated to be as high as 43% (Andrews *et al*., 1996; Childs, Mercer, & Childs, 1993). The implications of misdiagnosis in this patient population are far reaching: beyond affecting medical management protocols and prognosis, they also have the alarming potential to incorrectly inform end-of-life decision-making (Graham *et al*., 2015; Schnakers *et al*., 2009; but see Wilkinson, Kahane, Horne, & Savulescu, 2009). A proposed solution to this problem is to incorporate functional neuroimaging protocols used to diagnose patients with DOC. Measures of neural activity provide a more sensitive means to evaluate perceptual function (Boly *et al*., 2005; Boly, Damas, & Lamy, 2004; Laureys *et al*., 2000), residual cognitive capacity (Menon *et al*., 1998; Owen *et al*., 2002), and covert awareness (Cruse *et al*., 2011; Monti *et al*., 2010; Owen & Coleman, 2008) than conventional behavioural methods. Routine assessments of neuronal integrity and neural function in this patient population could greatly improve diagnostic accuracy and advance the understanding of the specific functional impairments observed in DOC (Owen, 2013).

Neuroimaging in Disorders of Consciousness

Following severe brain injury, standardized measures of awareness evaluate a patient's ability to respond to environmental triggers and, specifically, to verbal commands. Command-following demonstrates a capacity to process sensory information in a meaningful way (e.g., recognize speech and interpret its contents) and plan an appropriate response – two processes that cannot occur in the absence of awareness. However, during clinical assessment, these capacities are contingent on behavioural output, which can be difficult for some patients and impossible for others. Serious brain injury may result in a cascade of associated impairments including: perceptual dysfunction and cognitive disorders such as aphasia, either of which could impede a patient's comprehension of the task, as well as paralysis, which would prevent a motor response altogether (Di Perri, Stender, Laureys, & Gosseries, 2014). To bypass this requirement, Owen *et al*. (2006) developed a motor imagery paradigm that used functional magnetic resonance imaging (fMRI) to measure neural, rather than behavioural, indices of command-following.

Covert Command-following

Imagined motor imagery produces robust, reliable patterns of neural activity that are unique to the imagined behaviour and are nearly identical to the patterns produced by physically making the same motor sequence (Kosslyn, Ganis, & Thompson, 2001). By capitalizing on the property that imagery and sensory process are represented in a similar way in the brain, in a seminal study, Owen and colleagues (2006)investigated whether differential patterns of activity produced by imagining different behaviours could be used as a proxy for overt behaviour during command-following tasks. They measured blood oxygen level dependent (BOLD) activity in a group of healthy controls during two types of imagined motor sequences: tennis and spatial navigation. In the tennis imagery condition, participants visualized playing a vigorous game of tennis, whereas, in the spatial navigation condition, participants imagined walking through the rooms of their home. In this covert command-following task, Owen *et al*. found that tennis imagery produced significant BOLD activity in the supplementary motor area, whereas imagined spatial navigation recruited the parahippocampal gyrus, as well as the lateral premotor and posterior parietal cortices. Having established a criterion of brain activity in healthy controls for each imagery condition, Owen *et al*. used this new paradigm to test one patient who met the clinical criteria for being in a vegetative state: she remained behaviourally unresponsive with preserved sleep-wake cycles five months after suffering traumatic brain injury. Despite this diagnosis, her neural response was identical to that of healthy controls during the imagery tasks, demonstrating unequivocally that she was capable of command following, a sign of awareness (Owen *et al*., 2006, 2007). This was an important result because, up to this point, the findings of earlier neuroimaging studies were only suggestive of the potential for some patients in a vegetative state to retain a degree of awareness (Menon *et al*., 1998; Owen *et al*., 2002). However, this fMRI-based motor imagery task was the first to provide clear evidence of this. In comparison to stimulus-evoked responses which can occur automatically (e.g., speech detection, face perception), motor imagery requires active participation and a level of functional involvement that is impossible without awareness (Owen *et al*., 2007; Owen & Coleman, 2008).

This paradigm was later adapted by Monti *et al*. (2010) to determine whether it could be used to form a binary system of communication for patients with DOC. They mapped the words “yes” and “no” to the tennis and spatial navigation imagery tasks and instructed participants to respond to a series of factual questions by visualizing the corresponding imagery type. Monti *et al*. first scanned 16 healthy participants and asked them to imagine both imagery types for 30s followed by 30s of rest. This was repeated five times and counterbalanced between trials to ensure an accurate and reliable differentiation between both imagery conditions as well as resting BOLD activity. Monti and colleagues then tested this procedure in a sample of 54 patients with DOC. They found that five of the patients (9%) could willfully modulate their neural activity in response to the task instructions (i.e., demonstrated command-following). Of the five, one patient, previously diagnosed as being in a vegetative state, used this technique to correctly answer nearly 85% of the questions posed to him by the researchers. Additional bedside testing revealed some behavioural signs of awareness in three of the patients who could perform imagined motor imagery.

The same principles used to test covert command-following in patients with DOC can also be found in other neuroimaging modalities, such as EEG. In a line of research parallel to fMRI-based assessments of awareness, Cruse *et al*. (2011) designed an imagined motor movement task to test cover command-following in patients using EEG. In this study, Cruse and colleagues trained a group of healthy volunteers on two types of imagined motor movements: squeezing their right-hand and moving their right-toes. Using a 25-channel EEG montage, they determined whether these simple imagined movements could be used to infer covert command-following. In EEG, imagined motor movements can be measured by event-related desynchronizations (i.e., reduction in power; ERD) of the μ (7 – n Hz) or β frequency bands (n – 30 Hz) over areas of the scalp contralateral to the side of the imagined movement. For instance, imagined movement of the right-hand results in an ERD over the left lateral premotor cortex, whereas imagined movement of the right-toes produces an ERD over the left medial premotor cortex. Cruse *et al*. recorded EEG from the healthy control group during the two imagined movement conditions and trained a classifier to differentiate between the two conditions using neural activity alone. After determining that the classification accuracy for both conditions was significantly above chance, they tested this procedure on a cohort of 16 vegetative state patients. Cruse *et al*. found that three of the patients tested (19%) responded appropriately to each of the imagined movement conditions (but see Goldfine, Victor, Conte, Bardin, & Schiff, 2011). With the success of this analysis, Cruse *et al*. (2012) set out to optimize this protocol to be as ergonomic as possible for patients with DOC. Cruse and colleageus modified their original experiment to work with a 4-channel bipolar EEG montage and measured imagined left and right-hand movement, rather than imagined hand-squeezing or toe-moving. Using similar analyses, Cruse and colleagues detected imagined motor movement in one patient who was consistently diagnosed as being in a vegetative state for 12 years after suffering traumatic brain injury.

Across four studies, imagined motor imagery paradigms were used to establish covert awareness in a small but significant number of behaviourally unresponsive patients. However, despite this success, the number of patients who demonstrated covert command-following was considerably lower than the estimated rate of misdiagnosis in this population (Andrews *et al*., 1996; Childs *et al*., 1993). However, a recent meta-analysis reported that the prevalence of covert command-following among patients in a vegetative state is approximately 14%, compared to the approximately 19% discovered by Cruse *et al*. (2012). Among patients in a minimally conscious state, the rate of response during these tasks increases somewhat to 32%, but this is still less than would be expected given that these patients are likely aware (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2016). One potential explanation for this discrepancy, is that the demands of these tasks may exceed the cognitive abilities of many patients with DOC, irrespective of their level of awareness. Potential sensory impairments notwithstanding, covert command-following requires extended periods of sustained attention, functional working memory, and effortful decision-making to perform successfully. Deficits affecting any one of these faculties can render a patient unable to respond to the task (Monti *et al*., 2010; Naci & Owen, 2013). To address this limitation, more recent efforts have moved away from "active" task-based assessments of awareness to, instead, examine neural activity during more natural conditions using engaging, real-world stimuli like movies. Naturalistic paradigms such as these are better-suited for patients with DOC because they have fewer constraints than covert-command following tasks, are designed to more easily capture and sustain attention, and do not require formal responses, thereby making them less demanding and difficulty for patients (Naci, Cusack, Anello, & Owen, 2014; Naci, Sinai, & Owen, 2015).

Naturalistic Paradigms

Experimental paradigms which use naturalistic stimuli require a somewhat unique mode of analysis to uncover the neural underpinnings of naturalistic processing. Rather than interrogate the areas of the brain which respond to temporally discrete stimuli or events, the continuous nature of naturalistic stimuli like movies requires some way to anchor the associated neural activity both in time and between people. One way to accomplish this is to quantify the spatial and temporal similarity of the neural response between participants during the same naturalistic stimulation. An fMRI analysis procedure has been developed to measure this inter-subject neural "synchronization" during movie-watching (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). This technique, first developed by Hasson *et al*. (2004) as well as Bartels and Zeki (2004a, 2004b), extracts the time course of a given voxel in one subject and uses this to predict activity in the corresponding voxel in another subject. Significant correlations between voxels suggests that these areas are synchronized across subjects. Originally, Hasson *et al*. tested this analysis using fMRI data collected from five healthy participants while they watched a clip from the movie "*The Good*, *The Bad*, *and The Ugly*" (1966). They found that, on average, nearly 30% of the cortical surface was synchronized between subjects during the movie. This included most of the primary visual and auditory areas, as well as somatosensory and multimodal association cortices, and regions of the cingulate gyrus. In a control condition, no significant inter-subject synchronization was observed, ruling out the possibility that this analysis simply detected spurious or resting-state activity. Additionally, Hasson and colleagues were also able to calculate the mean correlation time course of the activated regions across all subjects, allowing them to track the degree of neural synchronization over time. The times at which the correlation peaked could then be used to reconstruct the events of the movie that drove this increase in synchronization (e.g., suspenseful or climactic events). This was the first study of its kind to demonstrate that complex temporally evolving naturalistic stimuli produce synchronized cortical responses across viewers. These findings have been replicated using different movies (Hasson, Malach, & Heeger, 2010), as well as auditory-only stories (Simony *et al*., 2016), and inter-subject neural synchronization has since been observed during natural speech (Zadbood, Chen, Leong, Norman, & Hasson, 2016), using different neuroimaging modalities (Dmochowski, Sajda, Dias, & Parra, 2012; Liu *et al*., 2016).

Naci *et al*. (2014) extended this analysis procedure to not only detect regions of significant inter-subject synchronization, but to determine which cortical networks code different aspects of the movie-watching experience. First, Naci *et al*. analyzed inter-subject neural synchronization using fMRI data acquired from 12 healthy volunteers while they watched a clip from the Alfred Hitchcock movie "*Bang! You're Dead*" (1961). This short film depicts a young boy who replaces his toy gun with a real one that he found in his parents' bedroom. The story follows the boy playing with this gun (e.g., pointing it at other characters) and the viewers do not know, moment to moment, whether the gun is loaded. Alfred Hitchcock was renowned for his ability to use narrative elements, rather than the physical properties of the movie (e.g., audio volume), to create feelings of tension and suspense in his viewers. These feelings of suspense may be one factor that contributes to viewer engagement and may underlie the common conscious experience of movie-watching. Naci *et al*. hypothesized that regions of the brain that respond to the movie's plot (requiring executive processes), along with sensory driven areas would be synchronized spatially and temporally across viewers, and that this could then be used as benchmark of awareness with which to test patients with DOC. They scanned 12 healthy participants using fMRI while they viewed "*Bang! You're Dead*" and again during rest (i.e., no stimuli or task) which served as a control condition. Consistent with the findings of Hasson *et al*. (2004), Naci and colleagues found significant brain-wide synchronization across all participants in primary sensory and association cortices as well as in supramodal areas in the frontal and parietal lobes during the movie. No synchronization was observed during the resting state condition.

To test which areas of inter-subject synchronization were driven by the plot, Naci *et al*. (2014) presented a scrambled version of the movie to a second group of 12 healthy participants. The frames of the scrambled version had been segmented into 1s clips and rearranged in time, thereby removing any discernible narrative. Significant synchronization was also observed during the scrambled movie but only in visual and auditory sensory regions. A subtraction procedure was then applied to the maps of cortical synchronization during the intact and scrambled versions of the movie. When compared to its scrambled version, the intact movie produced significantly greater inter-subject synchronization in bilateral temporal regions and, importantly, widespread across the frontal and parietal cortices. Naci *et al*. proceeded to run a group-level independent components analysis (ICA) to separate these regions of synchronized activity into five spatially distinct functional networks: auditory, frontoparietal, visual, motor, and precuneus. Additionally, single-subject ICAs were performed to verify that the inter-subject synchronization observed at the group level for these networks was robust across all participants. A leave-one-out procedure revealed that the single-subject time courses of the independent components (ICs) were significantly correlated between individuals.

The frontal and posterior parietal lobes are known to support numerous higher-order "executive" functions including cognitive flexibility and inhibition (Collette *et al*., 2005; Duncan & Owen, 2000; Niendam *et al*., 2012), attentional control (Hampshire & Owen, 2006; Ptak, 2012), theory of mind (Rowe, 2001) and working memory (Keller, Baker, Downes, & Roberts, 2009; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005). While executive function and conscious experience are not identical, the engaging nature of movies may provide a practical bridge between the two. Naci *et al*. (2014) observed significant inter-subject synchronization in frontal and parietal cortices only during the intact movie, suggesting that its narrative and associated affective elements (e.g., tension, suspense) reliably activate these executive areas. To test this, Naci and colleagues performed two additional behavioural experiments to measure the executive demands of the movie and their effect on the frontoparietal executive network.

After isolating the frontoparietal network and its activity, Naci and colleagues quantified the executive demands of "*Bang! You're Dead*" using the Sustained Attention to Response Task (SART). The SART is a dual-task variant of the go-no-go paradigm. It provides a continuous measure of the executive demands of a primary task as a function of the changes in response characteristics (e.g., reaction times [RT], percent correct) of a secondary task whose cognitive demands remain constant. The SART assumes that executive function (e.g., attention, working memory, response inhibition) is a limited resource and, as such, significant reductions in performance on the secondary task are due to increased executive demands of the primary task. In their study, participants were required to attend to the movie (primary) while simultaneously responding to an auditory go-no-go task (secondary).

A group of 27 healthy volunteers were recruited to perform the SART outside of the scanner. These participants were instructed to provide a speeded key-press response when they heard specific "go" digits (numbers 1 – 7 and 9) but to withhold a response when they heard the "no-go" digit (number 8). Naci *et al*. retained the data from 15 participants who correctly performed the SART task and averaged their RT to generate a continuous measure of the movie's executive demands over time. They found that shorter reaction times (RT) frequently preceded an incorrect response to the "no-go" digit, demonstrating a shift towards response automaticity (i.e., reduced cognitive control) resulting from an increased executive load of the movie (Manly, Robertson, Galloway, &

Hawkins, 1999). They included the results from the SART as a regressor in their fMRI movie data and found that changes in RT significantly predicted the time course of activity in the frontoparietal network. Specifically, lower performance on the SART (i.e., higher executive demands of the movie) predicted increased activity in frontoparietal cortices.

In a follow-up behavioural experiment to qualitatively assess participants' subjective experience of the movie, Naci *et al*. (2014) asked participants to rate the degree of suspense for each scene. They recruited a third group of 15 healthy volunteers to provide suspense ratings from least to most suspenseful at 2s intervals for the duration of "*Bang! You're Dead*". Like the SART, suspense ratings provide a continuous measure of the executive demands of the movie. Suspense arises from processing the superordinate elements of the movie and using them to form and update a predictive model about each character's mental state, the potential consequences of their actions, and the possible outcomes of the narrative. Feelings of suspense suggest a significant engagement of executive resources (e.g., attention, working memory, theory of mind) that are necessary to successfully process the movie. Naci and colleagues found that the suspense ratings were significantly correlated between subjects, which suggested a similar conscious experience across viewers and, when added as a regressor to the fMRI movie data, suspense ratings significantly predicted activity in the frontoparietal regions.

Taken together, these findings provide strong evidence for the involvement of the frontoparietal executive network in movie-watching. Moreover, significant inter-subject neural synchronization of frontoparietal BOLD activity during the intact, but not the scrambled version of "*Bang! You're Dead*" suggested that participants were similarly engaged in the narrative and supramodal features of the movie and not simply responding to its auditory or visual properties. Naci and colleagues (2014) proceeded to test whether frontoparietal executive network activity elicited during the movie could serve as a marker of awareness in patients with DOC. In the last experiment of this study, Naci *et al*. presented "*Bang! You're Dead*" to two behaviourally unresponsive patients while recording their BOLD activity using fMRI.

Patient 1 had been rendered behaviourally unresponsive by progressive encephalopathy. Repeated bedside examination resulted in fluctuating diagnoses between a vegetative state and a minimally conscious state, depending on whether she performed visual tracking at the time of assessment. However, despite showing no behavioural signs of awareness accompanied by a low score of the CRS, perhaps it was possible to use brain activity to identify residual signs of awareness. Using the success of applying group-level ICs to reliably predict activity in the corresponding component in single subjects, Naci *et al*. (2014) applied this method to determine whether Patient 1 produced brain activity during the movie that resembled that of healthy controls. They found significant patient-group synchronization in auditory, but not visual or frontoparietal ICs. While this indicated that Patient 1 could process the auditory properties of "*Bang! You're Dead*", it remains unclear to what degree this information reached her awareness. Cortical reactivity to auditory stimulation has been reported extensively in this patient population, but often this activity remains local to primary auditory processing areas (Boly *et al*., 2004; Henriques *et al*., 2016; Laureys *et al*., 2000; Schiff & Plum, 1999).

Naci *et al*., (2014) applied the same technique to the fMRI data acquired from a second patient. Patient 2 had previously suffered hypoxic brain injury leading to coma. Three weeks after his injury, he regained sleep-wake cycles and was subsequently diagnosed as being in a vegetative state. However, like Patient 1, more recent behavioural assessments resulted in a vegetative state or minimally conscious state diagnoses depending on whether visual pursuit could be detected. The results of the analysis revealed significant patient-group synchronization in the auditory, as well as visual networks, and, crucially, in the frontoparietal executive network. Although frontoparietal engagement alone may be indicative of higher-order executive processing, Naci and colleagues also found that the time course of activity in this network significantly corresponded to the quantitative and qualitative measures of executive load collected from healthy controls (Figure 2).

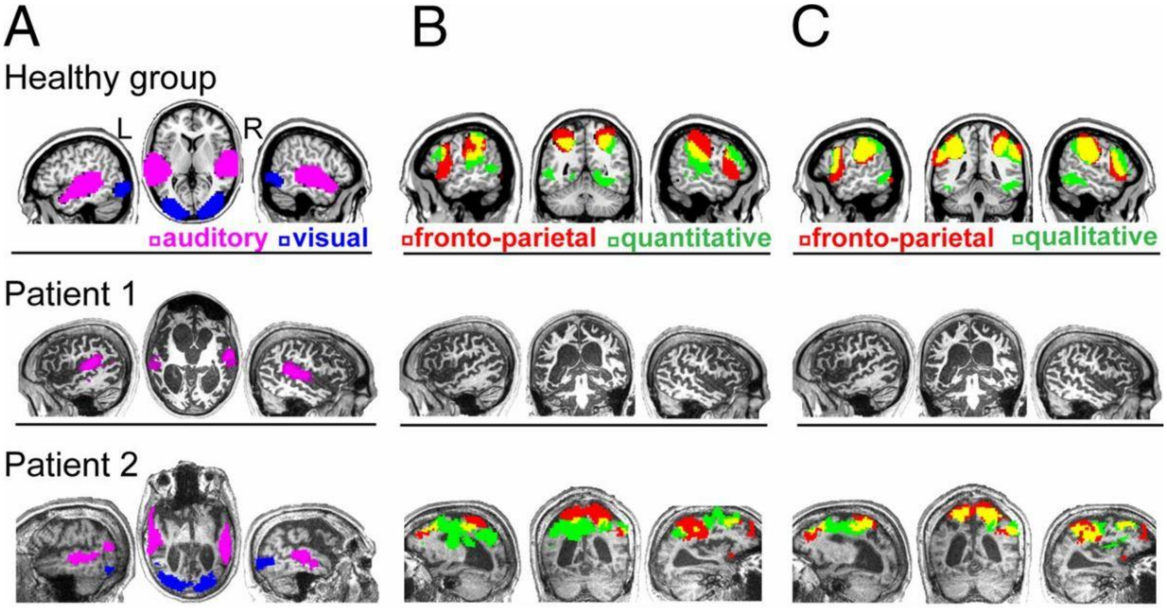

Figure 2. Auditory, visual, and frontoparietal ICs in healthy controls and patients with DOC. Quantitative and qualitative prediction of activity (green) and their overlap (yellow) with frontoparietal areas (From Naci *et al*., 2014).

The results from Naci *et al*. (2014) demonstrated that the uniformity of neural response across subjects during naturalistic stimulation can be used to infer, to some degree, the similarity of their conscious experience. While a subject's moment-to-moment contents of consciousness could not be decoded from neural activity alone, their ongoing engagement in the movie's narrative could be indexed both by activity in the executive network, comprised of frontal and parietal cortices, as well as its temporal correspondence with the evolving executive demands of the movie. When applied to two behaviourally unresponsive patients, this technique provided strong evidence that one could process, not only the physical properties of the movie, but its plot in a similar manner to healthy individuals. These findings demonstrate that using naturalistic paradigm are an especially powerful tool to assess awareness in patients with DOC; movie-watching does not require task instructions, behaviour, or responses of any kind which is ideal for this patient population. However, one of the findings from Naci *et al*. raises some questions regarding the design of this task. Both patients included in this study were diagnosed as being in a minimally conscious state prior to testing. Despite this, visual and frontoparietal synchronization was only observed for Patient 2. Auditory synchronization in Patient 1 suggested that she could process the auditory information of the movie similarly to healthy controls, but not its visual or narrative elements. This could be due to several factors, one of which relates to the movie's reliance on visual information to convey suspense. Perhaps this patient was conscious, but visual deficits limited the sensitivity of this movie to detect awareness. In fact, patients with DOC, because of their injuries, frequently present with considerable visual impairments (Naci *et al*., 2015). The inability to control their gaze, fixate on certain areas of the screen, or to process visual information altogether could limit the amount of narrative information a patient can derive from the movie, thereby preventing their engagement with the stimulus and the subsequent frontoparietal response.

A continuation of this study was conducted by Naci *et al*. (2015) to investigate whether naturalistic auditory stimuli alone could elicit similar frontoparietal executive processing. Auditory function is typically spared in patients with DOC and a paradigm that uses unimodal stimuli that rely on processing from the modality that is often intact, might therefore, be better suited for these patients. Naci and colleagues piloted two types of naturalistic auditory stimuli in a group of 15 healthy controls while recording their neural activity using fMRI. The first stimulus type consisted of two short suspenseful instrumental pieces. They hypothesized that the suspenseful tone of the music, in the absence of any speech or dialogue, may be sufficient to drive frontoparietal activity. The second type of stimuli was an audio-only clip from the movie "*Taken*" (2008). This clip depicts the kidnapping of a teenage girl and a subsequent phone conversation between the girl's father and her captor. The suspense of "*Taken*" builds as the narrative progresses, and is aided by the incorporation of building, ambient sound effects. A scrambled version of this clip was also used as a baseline condition. To analyze their data, Naci *et al*. employed the same analysis parameters used previously to detect neural synchronization while participants listened to the audio clip. During the musical pieces, inter-subject synchronization was limited to bilateral auditory cortices and did not extend to frontal or parietal regions. Conversely, the intact "*Taken*" clip produced significant brain-wide synchronization across participants, whereas the scrambled version produced synchronization in primary sensory and association cortices. A subtraction procedure between the conditions revealed significantly greater inter-subject synchronization in temporal, motor, frontal/pre-frontal, and parietal regions during the intact audio. Group-level ICA extracted several spatially distinct components of synchronized activity, including the frontoparietal executive network. The time courses of single-subject frontoparietal ICs showed significant correlations with the group-level component, and a leave-one-out procedure found that frontoparietal activity could be predicted from the group time course in all but one participant (93%). These findings suggested that auditory-only stories could be used in place of audio-visual stimuli to assess awareness in patients with DOC.

The Current Study

While the results of Naci *et al*. (2015) expand the applicability of naturalistic paradigms to test for awareness in behaviourally unresponsive patients, the use of fMRI in this population still presents a considerable challenge. Scanners are not widely available in hospitals or patient care centers and the financial costs associated with routine a scanning regimen prevent fMRI-based assessments from becoming standard clinical practice. Furthermore, patients with DOC often move involuntarily which contaminates fMRI data, and many patients, especially those who have suffered traumatic brain injury, have metal implants which preclude fMRI scanning altogether. EEG, on the other hand, can be administered at the patient’s bedside, has fewer exclusion criteria, and can capture rapid, transient changes in neural activity at a millisecond time-scale. In this sense, EEG provides an ideal alternative for assessing awareness in patients with DOC. The remainder of this thesis will evaluate the feasibility of capturing inter-subject neural synchronization in using the audio-only narrative from Naci *et al*. (2015) in a paradigm adapted specifically for EEG. From a pragmatic perspective, EEG is low-cost, portable, and easy to administer at the bedside. Perhaps more importantly, EEG provides a measure of neural activity at millisecond time scales, thereby capitalizing on the rich temporal dimension of naturalistic stimuli to capture precise moment-to-moment changes in inter-subject synchronization in the narrative. In Chapter 2, I will present and discuss the results from a control study in which I collected EEG data from healthy participants while they listened to the audio from “*Taken*” and analyzed the data using a novel inter-subject correlations technique designed to identify periods of synchronization by extracting configurations of neural activity that are most highly correlated between subjects (Dmochowski *et al*., 2012; Ki, Kelly, & Parra, 2016). This technique provides a continuous measure of inter-subject synchronization throughout the duration of the audio clip. In Chapter 3, I present findings whereby the patterns of activity observed in the cohort of healthy controls, including both the topographic pattern of activity on the scalp, along with time course of activity, served as neural benchmarks to detect awareness in patients with DOC who are behaviourally unresponsive. This analysis procedure was applied to EEG data acquired from a cohort of patients while they listened to the auditory narrative. The resulting neural activity was contrasted at the group-level between patients and healthy controls and assessed at the single-patient level to determine their degree of similarity to the healthy control group, thereby providing evidence for signs of conscious awareness.

Chapter 2: Indices of Inter-subject Neural Synchronization in EEG

Introduction

The goals of this chapter are twofold. The first is to present a novel EEG analysis procedure designed to capture inter-subject neural synchronization, resolved in time, during naturalistic auditory stimulation. Previous research has demonstrated that this analysis can detect global synchronization (i.e., overall synchronization over the course of the stimulus) generated by auditory stimuli but none has done so in a time-resolved fashion. This is a crucial point for the current study, as leveraging the temporal properties of inter-subject synchronization allows for a moment-to-moment comparison between healthy controls and patients with DOC (Cohen & Parra, 2016; Dmochowski *et al*., 2012; Ki *et al*., 2016). The second goal is to evaluate whether this technique is sufficiently sensitive to detect individual-to-group synchrony; that is, to quantify the degree of similarity between an individual and the rest of the group, in healthy control subjects during a naturalistic audio-only paradigm. If robust, this contrast could then be extended to evaluate the degree to which patients with DOC synchronization with healthy controls during this task, similar to the work of Naci *et al*. (2014).

EEG has been used extensively to test perceptual and cognitive function in patients with DOC, and many EEG paradigms have been designed to test for awareness at the bedside. Covert command-following tasks have been adapted for use in EEG (Cruse *et al*., 2011, 2012) and event-related potential (ERP) techniques have been applied to assess awareness based on the presence or absence of specific EEG components, such as the P300, thought to underlie various higher-order cognitive functions (Beukema *et al*., 2016; Gibson *et al*., 2016; Kirschner, Cruse, Chennu, Owen, & Hampshire, 2015). However, traditional time-locked ERP analyses require many trials and consistent responses across them to extract a recognizable and significant component, thereby inflating the cognitive demands of the task, plus bedside measures of covert command-following are still subject to many of the limitations as those developed for fMRI (see Chapter 1). Moreover, as in fMRI, task-free EEG protocols that use naturalistic stimuli are better-suited for patients with DOC. The fine temporal resolution of EEG lends itself well to naturalistic designs; narratives evolve and unfold over time, and EEG affords the ability to track sensory and plot-related changes in neural activity over the duration of the stimulus. Therefore, an analysis procedure designed to compute time-resolved activity from EEG data acquired during naturalistic stimulation would be ideal to assess awareness in patients with DOC. One approach that is ideally suited to meet both goals is inter-subject neural synchronization.

One approach to calculating neural synchronization from EEG data acquired during naturalistic stimulation was developed by Dmochowski *et al*. (2012). In that study, Dmochowski and colleagues recorded EEG activity from a group of 10 healthy volunteers while they watched three short movie clips. Two of the clips were taken from the movies "*Bang! You're Dead*" and *"The Good*, *The Bad*, *and The Ugly"*, respectively. A third clip depicting a naturalistic outdoors scene was used as a control. The participants watched each movie clip twice and the EEG data from both viewings were used to calculate neural synchronization for each movie using a novel correlational procedure, what they call a correlated components analysis (rCA). This data decomposition method, similar to a principal components analysis (PCA), generates a set of spatial weights which maximizes the correlation between two group-aggregate data sets, in a pair-wise fashion. Like PCA, rCA outputs the same number of components as there are recording sources (e.g., 64 channel EEG would produce 64 components), and ranks them based on strength of correlation across the group by solving an eigenvalue problem, meaning considerably weaker correlations for later components. The three most correlated components for each movie were then used to calculate neural synchronization between participants (inter-subject correlation; ISC). To accomplish this, Dmochowski and colleagues back-projected the component vectors generated by the rCA into the raw data for each participant to derive a unique time series for each participant based on each component. They used this time series to calculate Pearson's correlations for all subject pairs using a sliding window of 5s with 4s of overlap. The correlation coefficients for all pair-wise comparisons were then averaged in time resulting in a mean correlation with a one second resolution for the duration of the movie. Significance levels for the correlation time course were determined using a permutation test approach; null distribution of correlation coefficients were created by scrambling one of the data sets in time and re-computing the analysis.

Recently, this analysis procedure has been extended to measure ISC during auditory-only naturalistic stimuli. Cohen and Parra (2016) used rCA to investigate whether neural synchronization could predict group-level memory performance and whether stimulus modality impacted ISC. They presented 10 short audio-visual movies to a group of 88 healthy volunteers (divided across the 10 movies) and measured ISC over time using the rCA. They also presented auditory-only, visual-only, and visual with scrambled audio versions of the movies to quantify the differences in group ISC for unimodal, multimodal, and scrambled naturalistic stimuli. Over all 10 movies, audio-visual stimuli elicited the highest ISC, followed by visual with scrambled audio, and visual only. Auditory naturalistic stimuli generated the lowest overall ISC across participants. This reduction in global ISC for audio-only narratives makes sense, given the significant amount of cortical surface devoted to visual processing and that unimodal stimuli necessarily recruit fewer regions of the brain than multimodal stimuli (Cohen & Parra, 2016). Still, the mean ISC for the audio-only condition was higher than chance levels, providing further evidence that rCA is successful at extracting components that reflect processing high-level information, most likely the plot. In fact, individual ISC (i.e., each subject’s synchronization with the group) were significantly correlated with performance on a follow-up memory task about the content of each narrative, suggesting that synchronization may reflect, to some degree, a participant’s engagement with the stimulus.

In Experiment 1 of the current study, rCA was used to calculate time-resolved ISC during naturalistic auditory stimulation in a group of healthy control subjects. Specifically, this analysis was applied to EEG data that was acquired while participants listened to intact and scrambled version of an auditory clip from Taken. In line with Naci *et al*. (2015), our goal was to determine whether ISC in EEG could be used to infer higher-order executive processing in healthy participants. The results from Cohen and Parra (2016) suggest that multimodal or unimodal visual stimuli maximize ISC between subjects but this is not a viable option for many patients with DOC (see Chapter 1). It is worth noting that, while naturalistic auditory stimuli generated the lowest mean ISC in their study, they were significant and reliably reflected engagement with the clip. However, the narratives used by Cohen and Parra differed substantially from those previously used to investigate inter-subject neural synchronization, which has never been assessed on the audio clip from the movie "*Taken*", which we used in the current study. This is important because the "*Taken*" clip used by Naci *et al*. is highly suspenseful and comes to a dramatic climax; it shares many of the same narrative properties as "*Bang! You're Dead*", which should strengthen the degree of similarity across participants. The auditory stimuli used by Cohen and Parra, on the other hand, consisted largely of short stories and monologues devoid of any narrative driven conflict giving rise to feelings of tension. This is a non-trivial matter given the ISC observed by Dmochowski *et al*. (2012) and Naci *et al*. (2014) tracked the supramodal elements of "*Bang! You're Dead*", specifically its suspense. rCA, when applied to a highly engaging auditory narrative like "*Taken*", may result in more robust ISC that are sensitive to plot-based changes in neural activity over time and may thus be ideal for testing awareness in patients with DOC.

Methods

Participants

Ethics approval for this study was granted by the Psychology Research Ethics Board of The University of Western Ontario (Appendix A). Eighteen graduate students from Western's Brain and Mind Institute were recruited to take part in this study (11 female, 7 male; 22 – 30 years). All participants were fluent in English, had normal or corrected-to-normal vision, and had no reported history of neurological disorder. Participants were compensated with $10.00 for one hour of testing. To more closely approximate the population characteristics of patients with DOC, no attempt was made to ensure right-hand dominance in this sample.

Stimuli

The stimuli used in this study were adapted from Naci *et al*. (2015). Two versions of a suspenseful audio clip from the movie "*Taken*" were presented to each of the healthy controls. The first version was the original narrative in its intact form. The intact clip depicts a phone conversation between a father and his daughter, who is away on vacation. During the conversation, it soon becomes clear that there are intruders in the house where she is staying. Shortly after this realization, the daughter character witnesses the intruders kidnap one of her friends. She begins to panic and is audibly terrified. The father character instructs her to hide and prepare to be kidnapped; he walks her through a series of instructions to prepare her for what will happen once she is found, and what she is to do to help him track down her captors. Towards the end of the clip, she is taken by the kidnappers and the audio is silent for a brief time. One of the intruders can be heard returning to the room and discovering the phone which is still on-call with the girl's father. The remainder of the audio consists of an intense exchange between the father and one of her captors.

The second version of the audio was a scrambled form of the narrative which served as a control condition. Unlike the scrambled versions of "*Bang! You're Dead*" used in previous studies in which discrete scenes of the movie were temporally rearranged, scrambling of "*Taken*" was accomplished through a spectral rotation of the audio frequencies. This rendered the speech unintelligible while preserving the acoustic properties of the stimulus (Green, Rosen, Faulkner, & Paterson, 2013). Each clip was 5m 04s in duration.

Procedure

Experimental design. Our intention was to design as simple a paradigm as possible in order to minimize its toll on patients with DOC. To that end, auditory stimuli were presented binaurally to participants at a comfortable listening volume through Etymotics ER-1 in-ear headphones. Stimulus presentation was controlled through the Psychtoolbox plugin for Matlab (Brainard, 1997; Kleiner *et al*., 2007; Pelli, 1997). Participants were seated in a dimly lit room and instructed to listen attentively to the both versions of the stimuli. The scrambled version of the "*Taken*" clip was presented first for all participants to limit any potential carry-over effects of the intact narrative.

EEG acquisition and preprocessing. EEG data were acquired with a 129-channel saline-electrolyte HydroCel^{TM} Geodesic Sensor Net system and a Net Amps 300 dense-array high impedance amplifier (Electrical Geodesics, Inc., OR, USA). The EEG signal was sampled at 250Hz and referenced online to the vertex (electrode Cz) using the Net Station 4.5.4 software package. Electrode impedances were kept below 50kΩ. All offline EEG processing was performed using MATLAB software and the EEGLAB toolbox (Delorme & Makeig, 2004). EEG data were re-referenced offline to the common average of all channels and filtered using a 0.5 - 60Hz digital finite impulse response (FIR) bandpass filter with a notch at 60Hz. Automatic artifact detection was used to identify channels with average amplitude variance two standard deviations above the mean. These channels were flagged for removal. Channels that met that criteria (*M* = 9.61, *SD* = 4.21) were replaced by interpolated signal from surrounding electrodes.

ICA was used to identify ocular artifacts (i.e., blinks and lateral eye movement), noisy channels, and muscular contamination in the data. Component rejection was performed manually for each participant in each condition. The mean number of components removed for the intact audio condition was 5.50 (*SD* = 2.21) whereas the number removed from the scrambled audio condition was 5.61 (*SD* = 1.88). Following ICA, the data was de-spiked following a method described by Dmochowski *et al*. (2012). This procedure identifies samples in the EEG where the squared magnitude of an electrode channel (i.e., its power) falls more than four standard deviations above its mean and replaces these samples with zeroes. De-spiking reduces the influence of excessive amplitudes on analytic component projection measures (a similar method is commonly used in fMRI analyses for removing artifacts). Additionally, to minimize the potential for muscle contamination in the rCA, channels on the neck, face, base of the skull, and around the ears were removed. Of the original 129 electrodes, we use 92 for the rCA.

Correlated component analysis. Group-level synchronization of BOLD activity has previously been used as a measure of the degree of similarity of perceptual and executive processing across a group of healthy participants (Hasson *et al*., 2004; Naci *et al*., 2015), and also patients with DOC (Naci *et al*., 2014). To measure inter-subject neural synchronization in EEG data acquired while participants listened to *“Taken”*, we ran a correlated components analysis. Originally developed by Dmochowski *et al*. (2012), rCA was designed to identify discrete patterns of electrode activity that are maximally correlated between subjects during naturalistic stimulation. These components serve a similar purpose to those extracted from fMRI data using group-level ICA, in that they reflect common neural activity across subjects and can be used to investigate group-synchronization over time. A more recent version of the rCA procedure, formulated by Ki *et al*. (2016), was used in this study.

rCA operates by relying on many of the same principles as PCA (or ICA), including many of the same assumptions. PCA is non-parametric multivariate dimensionality reduction technique used to extract meaningful information from large, complex data sets. Specifically, this analysis computes a new linear basis of orthogonal vectors which re-express the activity of a dynamic system in a way that captures the greatest amount of variance, while minimizing redundancy and noise (Shlens, 2009). For example, raw EEG data typically take the form of an $n \times t$ matrix where n is the number of electrode channels and t is time. This data matrix **X** is a measure of the temporal fluctuations of voltage at each electrode site relative to the reference. However, in this format, it is unclear which data best reflect the underlying neurophysiological processes of the brain. Indeed, gleaning substantive information from raw EEG data is difficult; the electrical signals recorded at the scalp are a mixture of neural activity and noise (e.g., cardiac artifacts, eye blinks, movement, and electrical contamination), significant covariation between electrodes adds redundancy to the data, and some electrode sites do not capture the dynamic activity of the brain as well as others. PCA provides a means to recover the meaningful dimensions of these data by computing a linear transformation of X to find orthogonal configurations of electrode activity that best explain the most variance. This is accomplished by computing an eigenvalue decomposition of the covariance of X. A standardized symmetric $n \times n$ covariance matrix $C_X = \frac{1}{n-1} XX^T$ is transformed by a mixing matrix W into a new subspace Y such that its covariance matrix $C_Y = \frac{1}{n-1} YY^T$ is diagonal. The eigenvectors w_i calculated for C_X are the principal components of X, and the diagonal eigenvalues λ_i of C_Y are the variances of X along W (Shlens, 2009). The principal components of X are ranked in descending order based on the amount of variance each can account for in the data. PCA computes $n - 1$ principal components which, in EEG, are represented as spatial weights of electrode voltages across the scalp and their corresponding time course.

rCA is computationally similar to PCA in that it computes an eigenvalue decomposition of covariance data, but where rCA differs is in the source of the covariance; rCA operates on the pooled within-subject cross covariance

$$\mathrm{R}_w = \frac{1}{N}\sum_{k=1}^{N} \mathrm{R}_{kk},$$

and pooled between-subjects cross covariance

$$\mathrm{R}_b = \frac{1}{N(N-1)}\sum_{k=1}^{N} \sum_{l=1,l\neq \mathrm{k}}^{N} \mathrm{R}_{kl}$$

where

$$\mathrm{R}_{kl} = \sum_{t} (\mathrm{x}_k(t) - \bar{\mathrm{x}}_k)(\mathrm{x}_l(t) - \bar{\mathrm{x}}_l)^{\mathrm{T}}$$

calculates the cross-covariance between participant *k* and participant *l* across all electrodes x at time *t*. The eigenvectors w_i of the cross-covariance matrix $\mathrm{R}_w^{-1}\mathrm{R}_b$, with the largest eigenvalues λ_i calculated as $(\mathrm{R}_w^{-1}\mathrm{R}_b)\mathrm{w}_i = \lambda_i\mathrm{w}_i$ are the components that maximize Pearson’s correlation between subjects in the data. Like the component ranking of PCA based on explained variance, components found using rCA are ranked-ordered by the magnitude of their correlation. The time courses and accompanying spatial weights of these correlated components represent patterns of evoked neural activity which are maximally correlated across all participants while listening to the “*Taken*” clip (Ki *et al.*, 2016). In the current study, pooled within and between-subjects covariances were computed separately for the intact and scrambled audio conditions. Only the top component extracted from each condition (i.e., the spatial weights and time course which maximized Pearson’s correlation in the group-aggregate data) was considered for further analysis here. Although components $i = 2 \ldots n$ undoubtedly encompass various aspects of the experience of listening to “*Taken*”, the top component reflects some neural processes that are most common across subjects and provides an optimal starting point to evaluate the utility of ISC as a means of capturing executive processing of the narrative.

Inter-subject correlation. To assess the reliability of the correlated component at the single-subject level, time-resolved ISCs were computed by back projecting the component vectors w_i into the original subject data to derive a component time course for each participant. We did this for each audio condition. With this per-subject time course, a measure of ISC encompassing the entire duration of the clip was computed first to quantify the magnitude of the correlation between each individual participant and the group and establish a distribution of synchronization in healthy controls; this is similar to the ISC analysis computed by Naci *et al*., 2015. To generate the distribution of ISCs, Pearson's correlations were calculated between all possible pairs of subjects using a sliding window technique. A sliding window of five-seconds with a three-second overlap was used to generate a correlation coefficient between pairs at two-second intervals over the course of the audio. This yielded 152 correlation coefficients for each of the 105 comparisons. The correlations computed for all subject pairs were then standardized using a Fisher's Z transformation and averaged at each time point to produce a mean ISC time course for the intact and scrambled audio conditions.

Statistical analyses. Non-parametric permutation statistics were used to test the significance of the group-averaged component time course for each of the two audio conditions. Null distributions of correlation coefficients were created by iteratively phase-shifting the computed component time course for each participant and computing mean of the pairwise correlations with the rest of the group for each of the 152 time windows (Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). We did this 1000 times to generate a null distribution of potential correlation values. The upper 5% of each null distribution was used as the significance threshold for each time point. Significance levels were adjusted for multiple comparisons using a false discovery rate (FDR) correction. The number of significant two-second time windows was then compared between the intact and scrambled conditions using a Chi-square test of proportion with an alpha level set to .05.

To test the spatial (dis)similarity of the component projections computed between audio conditions, a scalar (dot) product was calculated. The dot product of two electrode projection matrices yields a single scalar value which quantifies the degree of differences in the spatial distributions of all electrode activity across two component topographies. Broadly, the dot product denotes the Euclidean distance between two vectors. Large dot product values (e.g., values approaching 1 or -1) denote a high similarity between vectors trending in the same or the opposite direction. Low dot product values (e.g., approaching 0) correspond to a near orthogonality of the vectors and, subsequently, a low similarity between them (Jackson & Sherratt, 2004). Non-parametric scalar product contrasts were performed between the intact and scrambled audio conditions for the healthy control group in this study.

Results

Group-level Neural Synchronization during Naturalistic Auditory Stimulation in Healthy Controls: Intact Audio Condition

The data from three participants were excluded from further analyses due to excessive channel amplitude variance throughout their EEG recordings. rCA was applied to group-aggregate EEG data acquired from $N = 15$ healthy participants while they listened to the intact version of "*Taken*". Our goal with this analysis methodology was not to establish statistical criteria for subject-to-group synchronization during the audio, but rather, to create a distribution of ISC across a group of healthy participants, effectively establishing a "zone" of healthy synchronization with which to compare to patients with DOC. Some variability is expected between individuals in the way they process and engage with the clip so, in order to make accurate and reliable claims about patients, it is important to position their neural activity relative to a group of people who process it in different ways. The resulting correlated component projection is presented in Figure 3a. The distribution of electrode activity showed a posterior occipital/parietal positivity and a distributed frontal and temporal negativity. A global measure of ISC was then computed to quantify the degree to which single participants are synchronized to the rest of group on this component. Per-subject global ISC are presented in Figure 3b. The degree of individual-to-group ISC ranged from .004 to .031 ($M = .016$, $SD = 0.007$) for the entire audio clip, with all but Participant 11 falling within a similar range. Although measures of global ISC can be useful in characterizing the distribution of synchronization across participants in a particular audio condition, ISC resolved in time affords the ability to track changes in group-level neural synchronization over the course of the narrative.

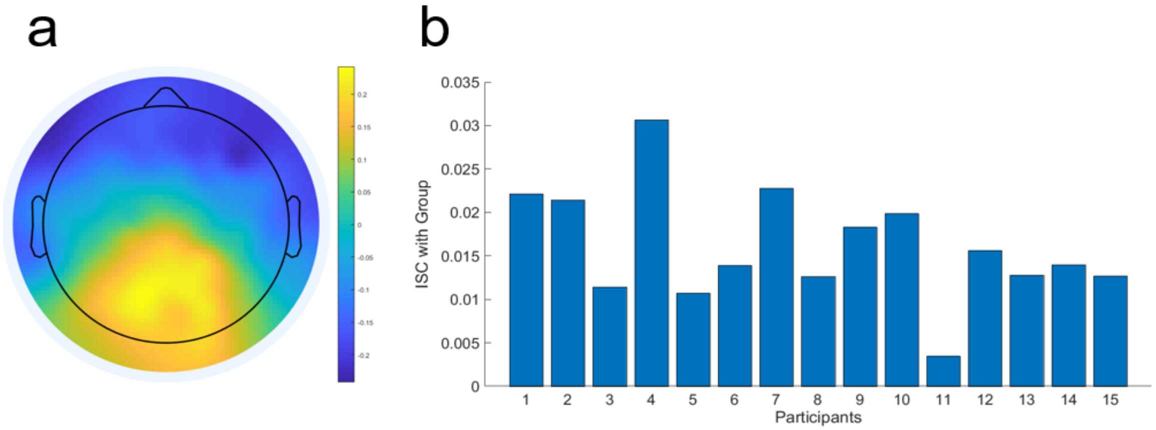

Figure 3. rCA component projection and global ISC during the intact audio condition. a.) The topography of electrode activity which maximized Pearson’s correlation between subjects. b.) Magnitudes of individual-to-group ISC across participants over the duration of the clip.

Time-resolved Pearson’s correlations were calculated between all subjects using their unique rCA component time courses. The correlations were then averaged at each time point to generate a mean time course of inter-subject synchronization for the intact audio condition. The group-average ISC time course is presented in Figure 4. Overall, the mean ISC was significant during 33 of the 152 time windows (21.7%) for the intact audio condition ($p < .05$, FDR corrected). This equates to a total of 1m 06s of inter-subject synchronization. Periods of significant ISC ranged from 2s (one time window) to 10s ($M = 5.50$, $SD = 2.58$). The group-average ISC values fell within -.01 ($p > .05$, FDR corrected) to .13 ($p < .05$, FDR corrected). The significant peaks in the mean ISC time course were grouped into 12 distinct periods (peak numbers in Figure 4). The time points and length of the significant periods of inter-subject synchronization, as well as the auditory properties and narrative content of the stimulus at these points in time, are presented in Table 1.

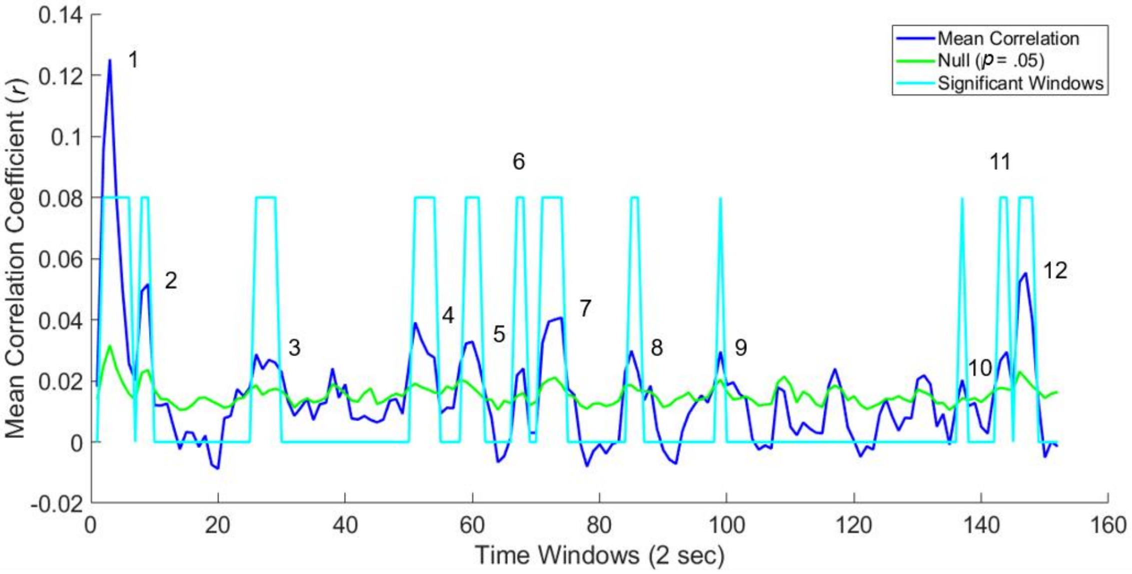

Figure 4. Mean ISC time course for the intact audio condition in healthy controls. The averaged inter-subject correlations (blue) plotted against the correlation coefficients which correspond to the top 5% of a randomly sampled null distribution (green). Windows of significant inter-subject synchronization (turquoise) outline the peaks in inter-subject synchronization. Peaks in ISC are numbered sequentially and correspond to the rows in Table 1 (below).

Table 1

Stimulus Features and Narrative Content during Significant ISC

Peak	(min:sec)	Narrative
1	0:04 – 0:14s	**Phone ringing** Beginning of a conversation between two characters (Mother and Father). First instance of dialogue.
2	0:16 – 0:20s	The remainder of the conversation and the sound of a phone hanging up.
3	0:52 – 1:00s	The middle of a second conversation between two characters (Father and Daughter). The father is nagging the daughter for not calling him after her plane landed in another country.
4	1:42 – 1:50s	After the intruders kidnapped the daughter's friend. The daughter is sobbing while telling her father what happened. The father is asking whether she met anyone on her trip.
5	1:58 – 2:04s	The daughter explains that she met someone when she got off the plane and they shared a cab to the place where she is staying. She says that she can hear the intruders coming for her.
6	2:14 – 2:18s	The daughter is trying to figure out how many intruders are in the house. She is sobbing while her father asks what room she is in.
7	2:22 – 2:30s	The father instructs her to hide under a bed in the next room. The daughter can be heard shuffling quickly across the room and under the bed.
8	2:50 – 2:54s	Kidnappers can be heard. The father asks daughter to move the phone so he can hear them. He instructs her to yell out everything she sees about the intruders when she is kidnapped.
9	3:18 – 3:20s	No dialogue. Footsteps can be heard getting closer and creaking the floorboards. Atmospheric sound effects accompany the footsteps.
10	4:34 – 4:36s	Part way through the father talking to one of the kidnappers. He says that he will find him.
11	4:46 – 4:50s	The latter half of the father's threat to the kidnapper. This is delivered in the style of a short monologue.
12	4:52 – 4:58s	There is a long pause before the kidnapper responds to the father. Atmospheric sound effects build to a climax.

Group-level Neural Synchronization during Naturalistic Auditory Stimulation in Healthy Controls: Scrambled Audio Condition

We also ran rCA on the group-aggregate EEG data acquired from the same *N* = 15 healthy controls while they listened to the scrambled version of "*Taken*". The resulting component projection is presented in Figure 5a alongside the component from the intact audio condition, displayed in Figure 5b. The spatial distribution of electrode activity showed considerable widespread negativity, with two small islands of moderate positivity: one in the left frontal areas and the other in the right posterior region of the scalp. A scalar (dot) product was calculated to quantify the coincidence of the component topographies between audio conditions. A dot product of -0.16 was found between the two component projection vectors which corresponds to a very low spatial similarity trending in inverse directions (Jackson & Sherratt, 2004).

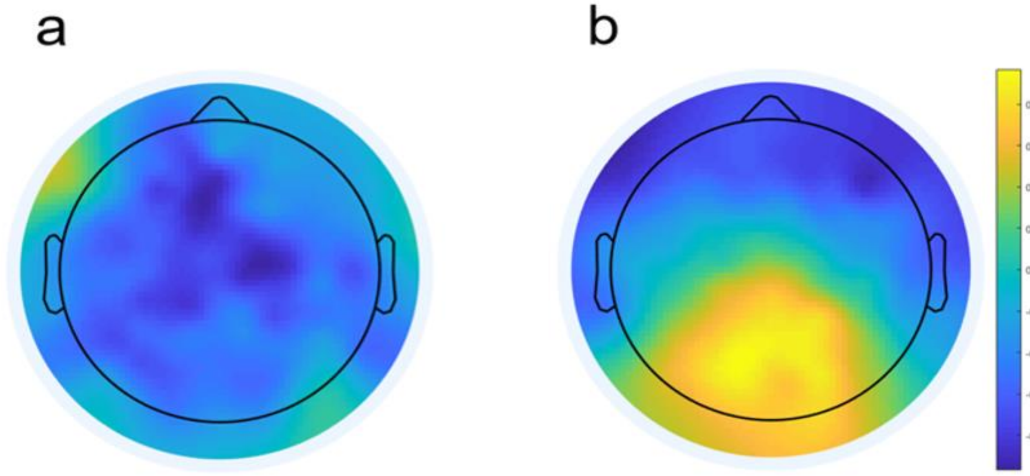

Figure 5. Contrast between the rCA components extracted during the scrambled and intact audio conditions. a.) The component topography observed for the scrambled audio condition. b.) The component topography observed for the intact audio condition.

Global ISC were calculated for this control condition and are presented in Figure 6b. The range of individual-to-group ISC was .005 to .025 (*M* = .014, *SD* = 0.006) and was similarly variable to the intact audio condition. The mean global ISC in this condition did not differ significantly from that observed in the intact audio condition, repeated *t*(14) = 1.22, *p* > .05. This highlights one of the strengths of the rCA procedure, namely, that it can identify and extract inter-subject synchronization linked to markedly different configurations of neural activity, such as the auditory-only component found here.

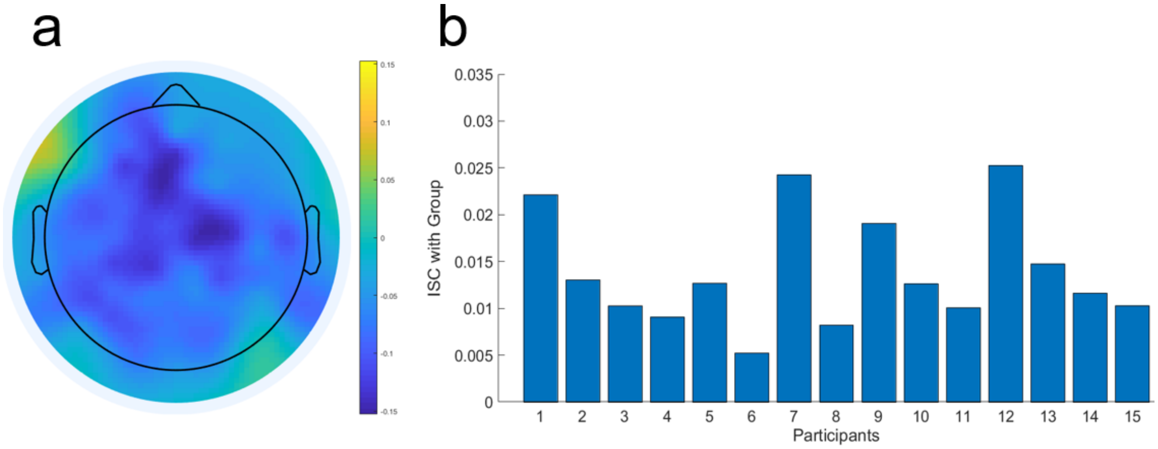

Figure 6. rCA component projection and global ISC for the scrambled audio condition. a.) The spatial topography of electrode activity which maximized Pearson's correlation between subjects. b.) The magnitude of individual-to-group ISC across participants for the duration of the scrambled audio.

The mean ISC resolved in time was calculated for the scrambled audio condition and is presented in Figure 7. Significant mean ISC were observed during 19 of the 152 time windows (12.5%), totaling 38s of inter-subject synchronization. This was significantly lower than the number of significant time points in the intact audio condition, $\chi^2(1, N = 152) = 4.52$, $p = .03$. The length of inter-subject synchrony ranged from 2s to 14s ($M = 4.75$, $SD = 3.99$). The mean correlation coefficients at each of the 2s time points ranged from -.01 ($p > .05$, FDR corrected) to .06 ($p < .05$, FDR corrected) and were, overall, significantly lower than the intact audio condition, repeated $t(151) = 2.12$, $p < .05$.

To ensure that the differences in component topographies and ISC observed between conditions were not due to chance, the rCA was recomputed on the intact audio data from $N = 13$ randomly selected healthy controls. This procedure was repeated iteratively 10 times and the results are presented in Figure 8. A similarity matrix (Figure 8a) was calculated by correlating the projection vectors of the first test component (Figure 8c, top left) with those of the other 9 components, each calculated on a different random sample. Overall, the component topographies (8a, c) and mean ISC time courses (Figure 8b) showed a considerable reliability across samples, supporting our earlier findings.

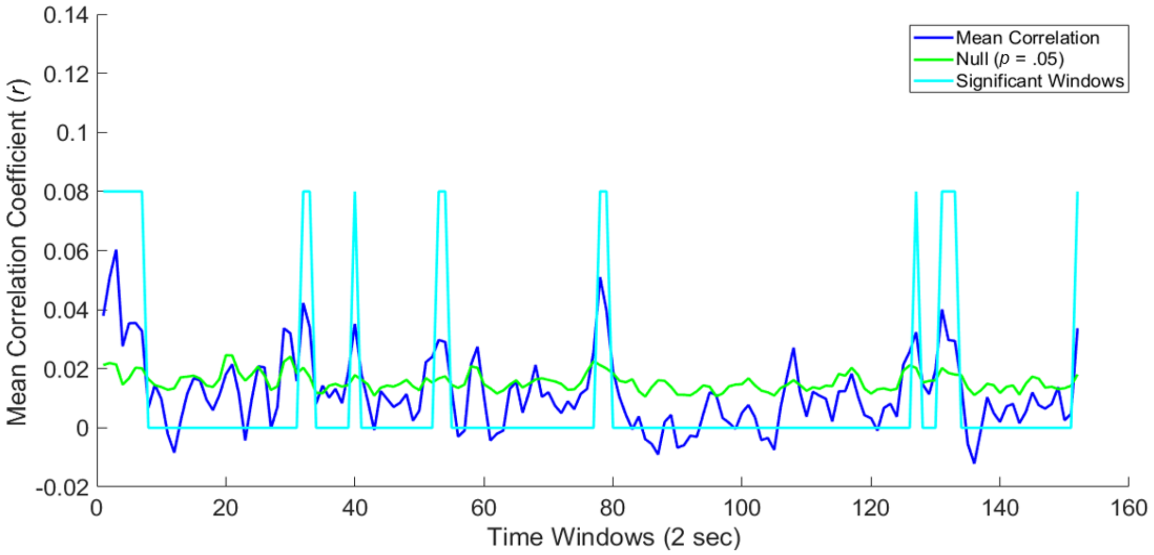

Figure 7. Mean ISC time course for the scrambled audio condition in healthy controls. The mean inter-subject correlations (blue), statistical significance thresholds (green), and windows of significant ISC (turquoise).

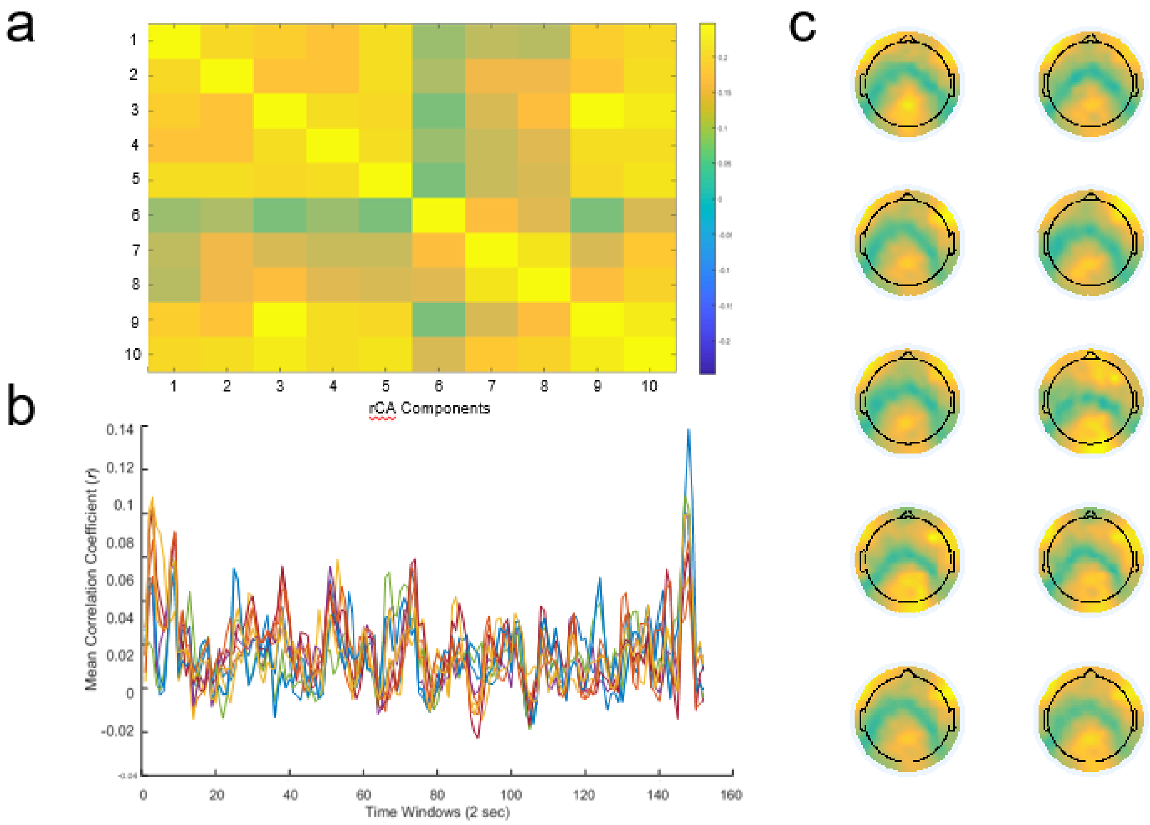

Figure 8. Reliability of the components extracted from rCA. a.) Similarity matrix of 10 components computed on N = 13 randomly selected healthy controls. Warmer colours indicate higher correlations. b.) The mean ISC time course for each component. c.) The resulting component projections.

Discussion

In Experiment 1, we were able to identify a reliable electrophysiological index associated with listening to an audio clip of *"Taken"* that is common to a group of healthy control participants. In line with the findings of Dmochowski *et al*. (2012), we could use rCA to track group-level synchrony over time and identifying periods of significant ISC, in a previously untested movie. Furthermore, these findings demonstrated that the rCA was sufficiently sensitive to differentiate between the two audio conditions. Indeed, in this study, the intact version of "*Taken*" generated significantly higher and more frequent neural synchronization between subjects overall compared to the scrambled version used as a control condition. This differentiation is especially important for two reasons: First, listening to a "scrambled" version of an audio clip drastically changes the way individuals process that information. Introducing variability in this way should result in less synchrony across participants (Dmochowski *et al*., 2012 and Ki *et al*., 2016). Second, from a theoretical perspective, the foundation of this task rests on the premise that the narrative of the stimulus requires higher-order processes that recruit executive areas of the brain, above those involved in primary and association sensory processing; evidence for conscious processing emerges when those become significantly synchronized between participants (Naci *et al*., 2014, 2015).

Does the synchrony we found reflect executive processing; that is to say, the same mechanism driving the results by Naci *et al*. (2014, 2015)? While it is impossible to say with certainty whether the results presented in Experiment 1 were due to the engagement of these additional areas, this is a plausible interpretation, since by removing supramodal properties, such as the narrative, by scrambling the audio clip, we found a significant reduction in group-level synchronization (Cohen, Henin, & Parra, 2017). What's more, the time points in which the mean ISC loses significance in the scrambled audio condition (i.e., points that were significant during the intact condition but not in the scrambled condition) largely coincide with moments that are critical to the development of the plot. For example, peaks 5 – 7 in the intact mean ISC time course (see Table 1) occurred after the initial discovery of the intruders, when the daughter character is talking to her father over the phone, trying to figure out who the kidnappers might be, how many she can hear in the house, and where she should hide. Following this, peaks 8 and 9 in the intact ISC time course at the quiet, tense moments preceding the daughter's eventual kidnapping. These points in the audio consist primarily of ambient sound effects, heavy breathing, footsteps, muffled dialogue from the intruders, and creaking floorboards. In the scrambled audio condition, these peak moments in ISC are wholly absent, likely owing to the indiscernibility of the dialogue and perhaps these subtle but a-contextual sound effects.

Previous studies by Naci *et al*. (2014) and Dmochowski *et al*. (2012) investigated inter-subject synchronization using a suspenseful audio-visual clip from the movie "*Bang! You're Dead*" in fMRI and in EEG, respectively. Both found significant and extensive ISC during the intact presentation of this clip but not for a scrambled version, which had its scenes shuffled in time to remove any semblance of a coherent plot from the movie. The authors of both studies attributed this reduction in synchrony to the removal of the narrative's meaning and, in the case of Naci *et al*., a disengagement of the frontoparietal executive network and the subsequent desynchronization of neural activity in this area between participants. In the present study, however, this line of causality is somewhat less straightforward, as the stimuli used between conditions differ in one important respect.

Unlike "*Bang! You're Dead*", whose scenes were temporally rearranged but ultimately kept in their original form, the clip from "*Taken*" was scrambled using spectral rotation. One consequence of this procedure, however, is that it diminishes the intelligibility of the speech in the audio while preserving its physical features. This property makes the intact and scrambled audio conditions differ by an additional, but important dimension - the presence of audible speech sounds. This is a pertinent difference because the signal properties of speech and non-speech sounds have been shown to be segregated neurologically as early as 100ms after stimulus onset, leading to a cascade of differential neural processes (Parviainen, Helenius, & Salmelin, 2005). As such, the disparities in ISC between audio conditions in the present study may reflect, in part, this difference in the sound profiles of the stimuli. Although this presents a challenge to the present study, and one that should be addressed going forward, it is worth noting that, in the pilot study for this paradigm, Naci *et al*. (2015) observed patterns of neural synchronization during the intact and scrambled versions of "*Taken*" that closely resembled those found by Naci *et al*. (2014) for the intact and scrambled versions of "*Bang! You're Dead*". A subtraction procedure contrasting regions of significant ISC between conditions revealed a striking similarity between studies, with a significant reduction in frontoparietal as well as temporal synchrony across participants during both scrambled conditions. Furthermore, the same regions of the brain remained significantly synchronized between participants during both scrambled stimulus conditions (e.g., primary and association auditory cortices), with the exception of early visual cortices for the audio only paradigm. What this suggests is that, while the linguistic discrepancy between audio conditions may alter part of the evoked neural response, this may only have a marginal additive impact on the larger effect of removing the narrative from the stimuli, as demonstrated by Naci *et al*. (2014). In this sense, speech may act more like a vehicle to present the story, the most salient feature of the stimuli, in these paradigms.

This may also be reflected by the relative similarities of the mean ISC time courses between both audio conditions in the present study. The overall mean ISC was shown to be significantly higher for the intact version of the audio than the scrambled version, yet the temporal structure of the peaks in ISC is somewhat comparable between conditions (see Figure 4 and Figure 7). For instance, both share an initial spike in ISC at stimulus onset, likely attributable to the sound of a phone ringing and the first instance of dialogue at the beginning of the stimulus, both see significant periods of ISC shortly after the 40s mark and approaching the half-way point of the audio, and each show a cluster of peaks in ISC towards the end of the clip. Naci *et al*. (2015) noted that the suspense of the "*Taken*" audio builds using a combination of speech and sound effects, such as atmospheric music and changes in audio volume. During the scrambled version of the clip, however, it was only the physical properties of the audio (e.g., its volume and saturation with sound over time) driving the observed ISC. Though, this may still reflect listener engagement, the behavioural marker generating shared conscious processing during naturalistic stimulation, to a certain extent. As outlined by Naci *et al*. (2014), naturalistic stimuli like movies and stories use a combination of features to create suspense and drive viewer or listener engagement, many of which are nonverbal. Tense-sounding background music or unsettling, atmospheric audio effects may still produce suspense, despite being out of context, which could, therefore, drive inter-subject synchronization. Since these audio features were originally coupled to the suspenseful plot of "*Taken*" the temporal correspondence in mean ISC between audio conditions does make sense. This also lends further support to the principal claim made here, that the reduction in synchronization during the scrambled condition was the result of removing the plot from the narrative. Shared moments of ISC between conditions show a marked decrease during the scrambled audio. The only difference between the two at these points in time is an overarching, coherent story.

In addition to serving as a control condition in this study, the scrambled audio may also provide a convenient measure of auditory function in patients with DOC. Several of the periods of significant synchronization observed in healthy participants appeared to cooccur with rapid changes in the auditory profile of the stimulus, such as the initial onset of the audio where a phone can be heard ringing or the loud moments shortly after the first kidnapping takes place in the story (around 1m 20s). Assessing an individual patient's synchronization with healthy controls (procedure outlined in Chapter 3) at moments like these may be sufficient to establish auditory processing. Furthermore, the frequency with which this patient-to-group synchronization occurs at predefined "loud" time points could also provide a measure of the degree of preserved auditory perception that does not require an additional task. Although this is not the primary goal of this thesis, the potential to extend this paradigm to address this question remains, and should be a focus of future work in this line of research.

The results from Experiment 1 also established the viability and utility of generating a temporal measure of inter-subject synchronization, as well as a global one, using rCA. Previous fMRI analyses used a leave-one-out procedures to correlate the synchronized group-level component time course to the BOLD component time course for individual subjects, achieving a metric of overall individual-to-group synchrony analogous to the global-ISC computed here (see Figure 3b and 6b; Naci *et al*., 2014, 2015). This provides a snapshot of the degree of engagement, a proxy for awareness, between participants during the task. However, each of us watch movies or listen to stories in slightly different ways. Despite these global measure of inter-subject synchronization, the idiosyncratic ways in which we engage with naturalistic stimuli are not captured with this approach. For instance, the points in time synchrony is highest, and when it is lowest, will not be detected in a static measure of inter-subject synchronization. While global ISC is sufficiently informative in fMRI, especially as it pertains to patients and the regions of their brains which become significantly synchronized to healthy controls, in the present study, global ISC alone collapses over the rich temporal information available both in the stimuli and afforded by EEG. Indeed, in Experiment 1, the mean global ISC did not differ significantly between audio conditions, despite the significant difference observed between the frequency of significant mean ISC (i.e., the number of significant time windows). This is almost certainly due to the fluctuations in inter-subject synchronization over time, which are muted by the measure of overall global ISC.

While the rCA was designed to track group-level synchronization over time, it also contains metrics to calculate synchronization on an individual level. However, the work in this field has, to date, focused solely on group-level differences (Cohen & Parra, 2016; Dmochowski *et al*., 2012; Ki *et al*., 2016). My thesis capitalizes on these available metrics to examine the degree to which individuals, including patients with DOC, synchronize with, or differ from, the rest of the group during naturalistic auditory stimulation. In doing so, it is then possible to track neural synchronization between individual patients and healthy controls, as well evaluate where they fall relative to each other participant's synchrony with the group. Like the global ISC measure from my first experiment, this provides a range of synchrony to compare across individuals and, importantly for Chapter 3, patients with DOC.

This was the goal of the experiment I conducted which I will present in the next chapter, where I extend the current procedure conducted in a group of healthy controls to a cohort of patients with DOC. Specifically, I asked whether the pattern of electrophysiological activity extracted from the group of healthy controls can serve as an index to detect residual awareness in patients? Unique to this study, both global and time-resolved measures of ISC were calculated in Experiment 2 to assess patient-to-group neural synchronization during the intact version of the "*Taken*" audio. Like Naci *et al*. (2014), the degree of synchronization will be analyzed at the group level and on a per-patients basis in an effort to quantify some aspect of their executive processing capacity, relative to healthy controls. If the rCA and its corresponding analysis methodology prove to be a suitable means to index neural synchronization in patients with DOC, it may provide a portable, rapid bedside diagnostic tool to assess awareness in patients with DOC.

Chapter 3: Neural Synchronization as a Measure of Executive Processing in Patients with DOC

Introduction

The aim of this chapter is to investigate whether rCA can be used as an effective means of assessing executive processing, as a proxy of awareness, in patients with DOC. In the results presented in the previous chapter, I demonstrated that rCA could successfully differentiate between the intact and scrambled naturalistic audio conditions based on their respective component topographies, time windows of synchronized neural activity (i.e., when participants were significantly correlated and for how long), and the magnitude of this synchronization in healthy controls. It was previously suggested that this distinction between conditions reflected, in part, a loss of meaning in the scrambled version of "*Taken*", analogous to the findings of Naci *et al*. (2015). If this is indeed the case, the degree of inter-subject synchronization found at different time points during the intact audio condition could serve as a marker of healthy executive processing of the narrative which could then be used to compare to patients with DOC. Patients whose neural activity synchronizes significantly with healthy controls' at key moments of plot development during "*Taken*" (see Table 1, Chapter 2) may be processing the superordinate properties of the audio (e.g., its plot and suspense) in a similar way. In Experiment 2, a cohort of patients with DOC was tested using the same naturalistic auditory paradigm and rCA method presented in Chapter 2, in order to determine whether we can detect residual signs of awareness in patients with DOC. The analysis parameters of this follow-up experiment are briefly outlined here, and fully discussed alongside the results of Experiment 2 in the following sections of this chapter.

In the previous chapter, two measures of ISC were computed using rCA: global ISC, which provided a metric to compare the overall correlations between each participant and the group by encompassing the entire duration of the audio clip, and the mean ISC time course which was used to track the time points at which significant inter-subject synchronization occurred during the "*Taken*" audio. In Experiment 2, we first applied both measures at the group level to a cohort of patients with DOC. The global ISC and the time-resolved ISC were used to investigate whether any aspect of the neural response elicited by the "*Taken*" audio was significantly correlated between patients. Despite their varying etiologies, diagnoses, and time post-injury, patients who may have residual forms of conscious awareness, but have no way of showing it, may synchronize to some degree while processing the auditory properties of the stimulus, the speech sounds, the dialogue, its narrative, or to any combination of these features. If this is the case, we would be able to conclude that patients are experiencing the narrative to a similar degree to a group of healthy participants; in other words, they share similar conscious experiences. Calculating group-level ISC with DOC is one method to quantify the overall similarity between patients with DOC and healthy controls in this task.

In addition to group-level analyses, the rCA can also be extended to compare single patients to healthy controls on a per-patient basis. To achieve this, the rCA is computed on the healthy control data with the addition of the EEG data from a single patient. The addition of a patient reconfigures the spatial weights of the correlated components, generating a new set of individual component time courses and, subsequently, a new measure of ISC for each healthy participant and for the patient. The logic behind performing the analysis in this way is that, the more similar a patient's experience is to healthy controls' while they listened to the audio clip, the more similar the pattern of evoked activity will be and, as such, the less the rCA output should differ after introducing a patient or any new data set. This is a relatively unique approach to testing patients with DOC but it is one that allows for an in-depth assessment of the utility of rCA both as a novel EEG analysis procedure and as a diagnostic tool.

To date, only a small number of studies have used rCA to track inter-subject neural synchronization during naturalistic stimulation and none have employed this analysis to test executive processing in patients with DOC. It remains a considerable challenge to identify stable, reliable, and common patterns in the EEG signal across a group of healthy participants to use as a benchmark of executive processing, to detect similar patterns of activity in patients, and to determine the extent to which overlapping patterns reflect some degree of conscious awareness (Dmochowski *et al*., 2012; Naci *et al*., 2015). Moreover, the electrophysiological manifestations of executive processing may be distributed across multiple components or exist in somewhat different spatiotemporal configurations between people, or, more likely, they could function in a fragmented form in patients who have suffered serious brain injury (Fingelkurts, Bagnato, Boccagni, & Galardi, 2012). To allow for some flexibility in this regard, rather than focusing on the exact dimensions of the components extracted from the healthy controls during the intact version of "*Taken*", the rCA was recalculated for each unique patient to maximize the probability of identifying a component that reflects some aspect of their narrative processing. With this, the spatial extent of the new component, its global ISC, and the mean ISC time course can be compared to healthy controls' in a similar manner to the between condition contrasts outlined in Chapter 2. Additionally, the time points at which each patient was significantly synchronized with the healthy group (i.e., time-resolved patient-to-group ISC) was calculated to provide a measure of their executive processing at specific time windows throughout the clip.

In this context, the group-average component topography, global ISC, and mean ISC time course not only provide an index of inter-subject synchronization but, with the addition of a patient, they represent a multi-tiered combinatory measure of patient-to-group synchronization during naturalistic stimulation, akin to Naci *et al*. (2014). In that study, the degree of patient-group synchronization in frontoparietal cortices was suggestive of a comparable level of executive processing of the narrative. Likewise, in the present investigation, significant patient-to-group ISC at meaningful time points in the audio (i.e., when the whole group is synchronized), on a component that resembles healthy controls' will be indicative of an analogous neural response to the audio and, perhaps, a similar degree of narrative processing.

Methods

Participants

Nine patients diagnosed with a DOC were recruited over the course of 12 months to participate in this study (3 female; 15 – 60 years). Informed consent was obtained from surrogate decision makers prior to assessment. All patients had been fluent in English prior to their brain injury. The CRS-R was administered as a behavioural assessment of perceptual and cognitive function on each day of testing (Kalmar & Giacino, 2005). Of the nine patients, seven met the criteria for a vegetative state diagnosis. Additionally, one patient met the criteria for being in a minimally conscious state, and one had previously been diagnosed with locked-in syndrome. These two were included in all group-level analyses because, despite their demonstrable awareness, they had both suffered a severe brain injury and reflect the variability in recovered awareness found in this patient population. Clinical and demographic data are presented in Table 2. The EEG data from three patients were selected for additional analyses at the single-subject level. These three were selected based on a combination of their etiologies, CRS-R scores at the time of testing, and, if applicable, the results from previous neuroimaging-based assessments. Their individual cases are outlined below.

Table 2

Patient Number	Age	Sex	Diagnosis	Etiology	Days Post Ictus	CRS-R Score
1	27	M	VS	TBI	3647	6
2	41	M	VS	Anoxic	1148	7
3	51	M	LIS	Stroke	1934	15
4	38	M	VS	Anoxic	7058	6
5	48	F	VS	TBI	8427	5
6	60	M	VS	Anoxic	2463	3
7	29	F	MCS	TBI	3252	8
8	21	M	VS	TBI	1349	2
9	15	F	VS	Anoxic	1072	6

Note. VS, Vegetative State; MCS, Minimally Conscious State; LIS, Locked-in Syndrome; TBI, traumatic brain injury; CRS-R, Coma Recovery Scale Revised (Kalmar & Giacino, 2005).

Patients 3 was a 51-year-old male who suffered a vertebral basilar stroke five years prior to participating in the present study. Following the acute stages of his injury, he was diagnosed with locked-in syndrome and was, therefore, fully aware (see Chapter 1 section 1.2). His latest CRS-R behavioural assessment, conducted in a long-term care facility on the day of testing, received a score of 15 out of a possible 23, owing to his inability to perform the necessary behaviour for some of the test items (Kalmar & Giacino, 2005). Nevertheless, he has retained some control over his eye movements which he uses as a form of binary (i.e., “yes” and “no”) communication. His data were selected for individual analysis in Experiment 2 because they represent a ground-truth of awareness with which to evaluate the ability of the rCA to identify executive processing in patients who have suffered severe brain injury.

Patient 5 was a 48-year-old female who suffered traumatic brain injury during a motor vehicle accident in 1993. Over the previous 23 years, she had consistently received a clinical diagnosis of being in a vegetative state. Her CRS-R behavioural assessment was conducted in her family home on the day of testing and was subsequently scored as a 5 out of 23 (Kalmar & Giacino, 2005). Previous fMRI-based assessments found evidence basic auditory function as well as some higher-order speech processing determined by a stronger BOLD response to speech than words. Activity was also observed in her supplementary motor area during imagined motor imagery, consistent with what is observed in healthy controls during this task. Despite this indication of covert command-following, she did not respond to the complementary spatial navigation task during the experiment. Additionally, a follow-up test using the same naturalistic stimuli and experimental parameters as Naci *et al*. (2014) found no evidence of frontoparietal activity in response to “*Bang! You’re Dead*”. However, a more recent paradigm developed by Naci & Owen (2013) was able to establish some binary communication using changes in BOLD response associated with attentional modulation. There was, therefore, some neurological evidence to suggest that this patient may have been, at least partially, covertly aware. For this reason, her data were selected for individual analysis in Experiment 2.

Patient 8 was a 21-year-old male who suffered a traumatic brain injury during a collision with a motor vehicle nearly four years ago. The GCS was used to test his responsivity at the time of the accident. It was scored as a 3 out of a possible 15 (Teasdale & Jennett, 1974). He had been clinically diagnosed as being in a vegetative state since his injury. His CRS-R behavioural assessment, conducted in a long-term care facility, was given a score of 2 out of 23 on the day of testing (Kalmar & Giacino, 2005). Patient 8 had not previously participated in a neuroimaging study of this kind. His data were selected for individual assessment in Experiment 2 because they represent the lower bound on the spectrum of behavioural responsivity observed in this sample (Kalmar & Giacino, 2005).

Stimuli

The stimuli used in Experiment 2 were adapted from Naci *et al*. (2015). They consisted of two versions of a suspenseful audio clip from the movie "*Taken*". The first was an intact version of the narrative - its contents have been described fully in Chapter 2, section 2.2. The second was a scrambled version of the audio which served as a control condition. Scrambling was performed by spectrally rotating the frequency profile of the intact audio, which rendered the speech unintelligible, thereby removing any discernable plot from the stimulus. Both versions were presented sequentially to the patients tested in Experiment 2. Each clip was 5m 04s in duration.

Procedure

Experimental design. EEG data collection for Experiment 2 took place in a private room at a long-term care facility or, alternatively, in the patient's home. Seven of the patients tested in Experiment 2 were seated in an upright position during the assessment, either in bed or in an accessibility chair. Due to physical constraints, Patient 8 remained in a supine position in bed for the experiment. Likewise, Patient 1 was transferred from a seated position in a chair to a supine position in his bed midway through testing to align with his daily routine. The CRS-R behavioural assessment was administered either directly before or shortly after the EEG portion of the experiment, depending on the patient's arousal level upon arrival. This decision was made with input from the family or at the discretion of the researchers. Stimuli were presented binaurally to each patient using Etymotics ER-1 sponge-tipped in-ear headphones. Stimulus presentation was controlled by Psychtoolbox for Matlab and presented through an Apple MacBook Pro running Mac OS X version 10.8.4 (Brainard, 1997; Kleiner *et al*., 2007; Pelli, 1997).

EEG activity was recorded first during the scrambled audio condition, followed by the intact audio condition for seven of the nine patients tested in Experiment 2. Like in healthy controls, presenting the scrambled audio first was intended to curtail any potential carry-over effects of the narrative. The order of the conditions was reversed for Patient 2 and Patient 7. This was deemed necessary at the time of testing based on the patient's temperament to maximize the likelihood of obtaining usable data for the intact audio condition. Data collection for a parallel EEG study took place during eight of the nine testing sessions reported here (for all but Patient 8). The two paradigms were counterbalanced between patient visits.

EEG acquisition and preprocessing. EEG data were acquired with a portable version of the 129-channel saline-electrolyte HydroCel^{TM} Geodesic Sensor Net system used in Experiment 1. The EEG cap was connected to a Net Amps 300 dense-array high impedance amplifier (Electrical Geodesics, Inc., OR, USA). The EEG was sampled at a rate of 250Hz and referenced online to electrode Cz (i.e., the vertex) using Net Station 4.5.4 running on a MacBook Pro with Mac OS X version 10.6.8. Electrode impedances were kept below 50kΩ during the experiment. EEG processing was performed offline using MATLAB and the EEGLAB toolbox (Delorme & Makeig, 2004). All data sets were processed separately for each patient.

EEG data were re-referenced offline to the common average of all electrodes and filtered using a 0.5 - 80Hz FIR bandpass filter. A notch filter was applied at 60Hz to remove line noise. Channels with an average amplitude variance two standard deviations above the mean were identified using automatic artifact detection. Channel removal was performed manually. Removed channels (*M* = 10.33, *SD* = 3.87) were replaced with data interpolated from surrounding electrode sites. The EEG was then epoched into 304s segments for both audio conditions. ICA was used to identify ocular and muscle artifacts in the data. Manual component rejection was performed for each patient and each condition separately. An average of 7.33 components were removed from the intact audio condition in (*SD* = 2.83) and 5.14 (*SD* = 2.19) were rejected from the scrambled audio condition. The data were then re-filtered between 0.5 – 60Hz and de-spiked (see Chapter 2, section 2.2 for details; Dmochowski *et al*. 2012). To limit the effect of muscle activity on the rCA, 37 electrodes around the face, neck, and ears were removed. The remaining 92 were included for all further analyses.

Group-level analysis procedures and statistical thresholds. The group-level analyses for the patient sample in Experiment 2 proceeded identically to those applied to the healthy control group in Experiment 1 (see Chapter 2, section 2.2 for full details). First, rCA was performed on the EEG data acquired from $N = 9$ patients with DOC while they listened to the audio clip from "*Taken*". This yielded a component topography that maximized Pearson's correlation between the patient EEG data concatenated in time (Dmochowski *et al*., 2012). The spatial weights of this component were then back-projected into the single patient data to extract a component time course with which to compare between patients in this sample.

The global ISC measure was calculated for each patient to derive an index of inter-subject neural synchronization over the entire length of the audio. Additionally, the mean ISC time course was generated by calculating Pearson's correlations between each patient pair at 2s intervals using a sliding window (5s window width with 3s of overlap) and averaging across all pairwise comparisons at each time point. Statistical significance thresholds were determined using the permutation test approach. A null distribution was created by phase-shifting the correlation coefficients calculated during the rCA and randomly sampling from them 1000 times at each 2s time bin. The magnitude of the correlation coefficient that fell at the 95th percentile of each of the 152 null distributions represented the threshold for statistical significance. This corresponded to an alpha level of .05 which was then adjusted using an FDR correction for multiple comparisons.

Per-subject analysis procedures and statistical thresholds. Individual patient assessments proceeded as an extension of the group-level analysis procedures applied to healthy controls (described in Chapter 2, section 2.2). Here, patients were individually added to group-aggregate data acquired from healthy controls to recalculate the rCA, thereby reconfiguring the spatial weights of the correlated components to incorporate the patient's neural response to the audio. This approach affords the ability to quantify deviations from the component projections and time course originally produced by a group of healthy controls after introducing patient data. This also allows for a direct comparison between individual patients and healthy controls, adding an additional level of analysis. Because of the novelty of this technique, a control analysis was performed using the data sets from *N* = 12 healthy participants and one generated from pure noise. This was to ensure that differences observed between groups (i.e., healthy controls and healthy controls plus a patient) or individuals were not simply due to changes in the signal properties of the additional data set. The results of this analysis are presented in Appendix B.

First, the group-level analyses, described previously, were recomputed after each unique patient was added to the healthy control group. These included: generating a new component topography, calculating the overall global ISC for each participant, and computing the mean ISC time course and its significance thresholds. This was followed by a novel calculation of the global ISC resolved in time for each participant and, importantly, for the patient. To achieve this, the global ISC was recalculated with the same sliding window used to create the mean ISC time course, using the same window size and overlap (described fully in Chapter 2, section 2.2). This resulted in an average individual (patient)-to-group correlation for each subject in 2s time bins.

This time-resolved version of the global ISC goes beyond the mean ISC time course to capture the moment-to-moment ISC between the patient and the rest of the healthy controls over the course of the audio clip. Additionally, having transformed global ISC into a temporal measure of inter-subject synchronization, the permutation test approach used to determine statistical significance thresholds in the mean ISC time course was similarly applied to identify significant periods of patient-to-group ISC. Null distributions were computed on a per-subject basis by randomly sampling the corresponding phase-shifted averaged individual-to-group ISC coefficients 1000 times at each time points. The 95th percentile of each of the 152 null distributions was the threshold for statistical significance at that point in time, reflecting significant patient-to-group synchrony (FDR corrected).

Results

Group-level Neural Synchronization during Naturalistic Auditory Stimulation in Patients with DOC

rCA and follow-up statistical analyses were performed on the group-aggregate EEG data acquired from *N* = 9 patients during the intact audio condition only. A significant percentage of the EEG data acquired from patients during the scrambled audio condition were heavily contaminated with noise and movement artifacts and, as such, could not be analyzed in the present study. The component topography found to maximize Pearson's correlation in these data is presented in Figure 9a and Figure 10a. In contrast to the one generated from healthy control data in the same audio condition (Figure 9b), this component displayed a net moderate negativity with sparse areas of muted positivity across the midline and parietal/occipital regions, as well as in the left frontal extent. A region of strong negativity was also found over the right frontal areas of the scalp. Visually, this component appeared to be comparable to healthy controls' during the scrambled audio condition (Figure 9c). However, dot product contrasts did not support this. The dot product calculated between the intact audio condition from patients and healthy controls was 0.28, whereas the dot product between the intact audio component from patients and the scrambled component for healthy controls was 0.11; this denoted a low similarity overall but nearly zero resemblance between the intact audio component from patients and the scrambled component from healthy controls (Jackson & Sherratt, 2004).

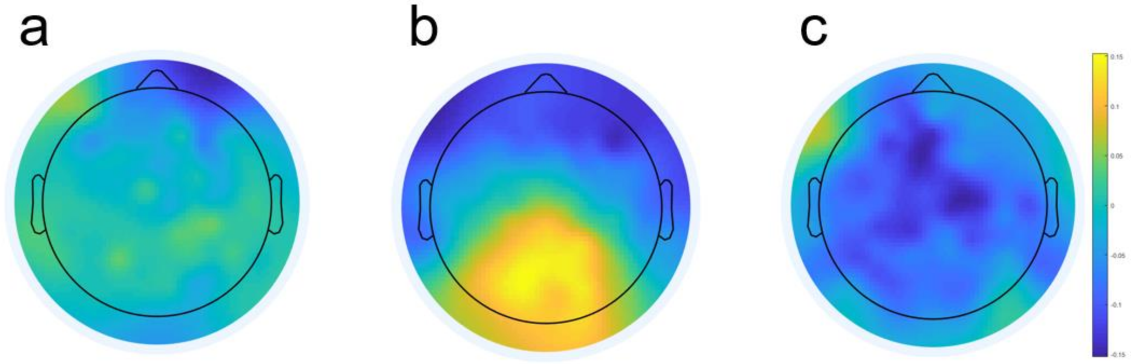

Figure 9. rCA component projections for patients and healthy controls. a.) The component extracted during the intact audio condition in patients with DOC. b.) The component from the intact audio condition in healthy controls. c.) The component from the scrambled audio condition in healthy controls.

The average magnitude of ISC between each patient and the rest of the sample was also calculated. Per-subject global ISC are displayed in Figure 10b. The individual-to-group ISC ranged from .006 to .064 ($M = .031$, $SD = .019$) with a greater variability between patients than healthy controls in the same audio condition. Interestingly, the mean global ISC in this sample was significantly higher than both the average ISC observed for healthy controls in the same stimulus condition, $t(22) = 2.77$, $p = .011$, as well as scrambled audio condition, $t(22) = 3.23$, $p = .004$. Time-resolved average ISC was also calculated at 2s intervals to measure group-level neural synchronization over the duration of the intact audio.

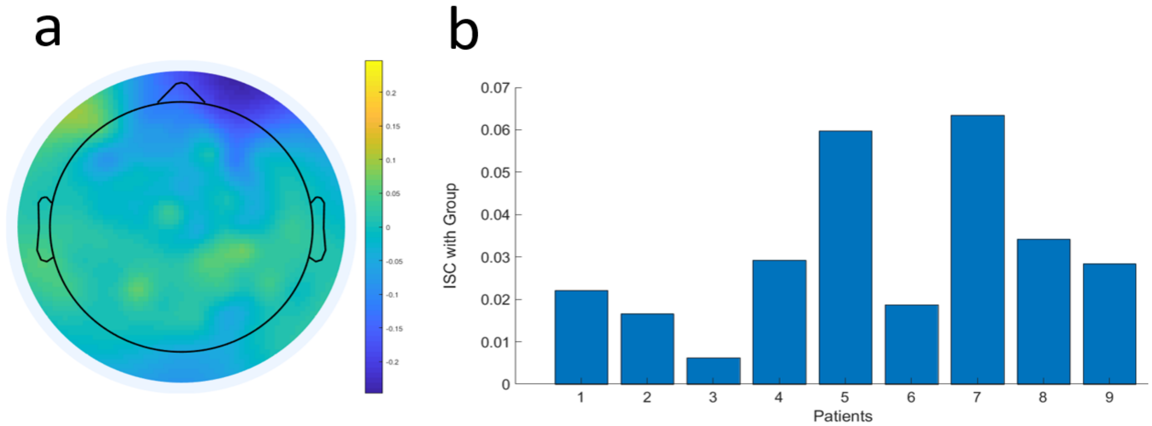

Figure 10. rCA component and global ISC for patients with DOC during the intact audio condition a.) The component topography which is maximally correlated between patients during the intact audio condition. b.) The magnitude of individual-to-group ISC across patients for the intact audio condition.

The mean ISC time course, significance thresholds, and significant time windows are presented in Figure 11. ISC between patients in this sample reached statistical significance in 6 of the 152 time windows (3.95%) or for a total of 12s. The total number of significant time points was significantly lower than the intact audio condition, $\chi^2(1, N = 152) = 21.35$, $p < .0001$, as well as the scrambled audio condition, $\chi^2(1, N = 152) = 7.35$, $p = .0068$ in healthy controls. The magnitudes of the mean ISC at each time point fell between -.048 ($p > .05$, FDR corrected) and .15 ($p < .05$, FDR corrected) and was significantly lower, on average, than the mean ISC in the intact audio condition, two sample. Significant inter-subject synchronization lasted between 2s and a total of 6s ($M = 4.00$, $SD = .030$).

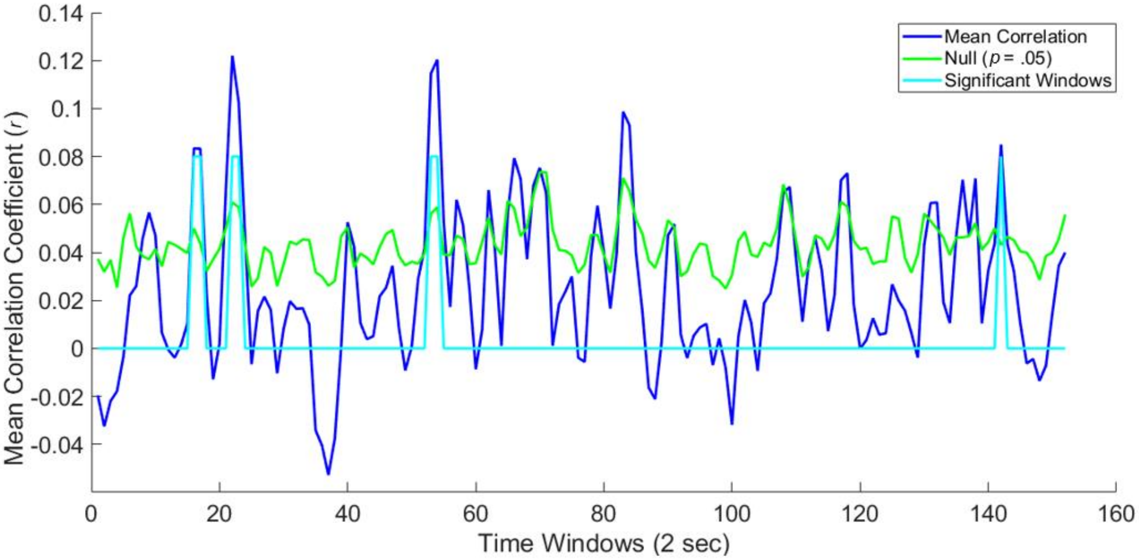

Figure 11. Mean ISC time course for patients with DOC during the intact audio condition. The averaged inter-subject correlations (blue) the correlation coefficients which correspond to the top 95th percentile of a randomly sampled null distributions (green), and windows of significant inter-subject synchronization (turquoise).

Individual Assessments of Neural Synchronization between Patients with DOC and Healthy Controls: Patient Three

Analyses of individual patients proceeded first with a recalculation of the rCA to incorporate their EEG data into the healthy control groups'. The rCA was applied to *N* = 16 EEG data sets acquired from 15 healthy individuals and Patient 3 (diagnosed with locked in syndrome; CRS-R = 15) while they listened to the intact version of the "*Taken*" audio. The new component projection is presented in Figure 12a. Its spatial topography bore a strong resemblance to healthy controls' intact audio component, consisting of a high-powered positivity spanning the frontal and temporal regions of the scalp, coupled with a distributed moderate-to-strong negativity over posterior parietal and occipital areas. Spatially, the component projection vector showed a high correspondence with healthy controls', dot product = 1.20, and was markedly dissimilar to both the scrambled audio component, dot product = -0.08, and component calculated for the patient group during the intact audio condition, dot product = 0.19 (Jackson & Sherratt, 2004). The global ISC for each healthy participant and Patient 3 is presented in Figure 12b. Individual-to-group synchronization ranged from .006 to .030 (*M* = .016, *SD* = .008) and Patient 3 ranked second in global ISC magnitude. The average global ISC observed in this sample was not significantly different from healthy controls alone in the same experimental condition, two sample $t(29) = 0.08$, $p = .94$, or in the scrambled audio condition, two sample $t(29) = - 0.81$, $p = .43$.

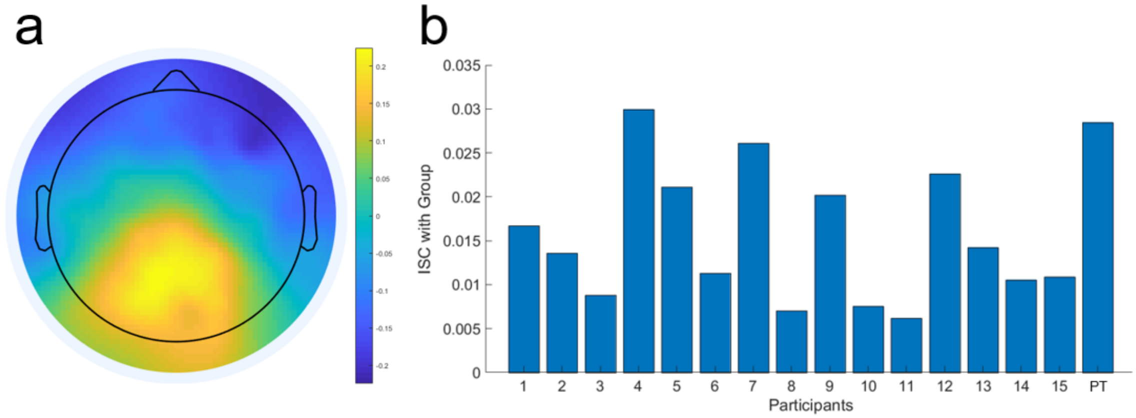

Figure 12. rCA component projection and global ISC for healthy controls and Patient 3 during the intact audio condition. a.) The topography which is maximally correlated between subjects in this sample. b.) Overall individual-to-group synchronization for Patient 3 (end) and healthy controls.

To assess group-level synchronization over time, the mean ISC was calculated in a time-resolved fashion on the healthy control EEG data and the data from Patient 3. The magnitude of the ISC at each of the 152 time points, the 95th percentile of the corresponding null distributions, and periods of significant inter-subject neural synchronization are displayed in Figure 13. The number of significant time windows dropped to 21 (13.82%; 42s of total synchrony), compared to healthy controls alone, but this was not a significant reduction, $\chi 2(1, N = 152) = 3.23$, $p = .072$, nor was it statistically different than the scrambled audio condition, $\chi^2(1, N = 152) = 0.12$, $p = .73$. The number of significant time windows in this sample was, however, significantly higher than the number observed in the patient group during the same audio condition, $\chi^2(1, N = 152) = 9.12$, $p = .0025$. The mean ISC values in this sample ranged from -.013 ($p > .05$, FDR corrected) to .061 ($p < .05$, FDR corrected), and periods of whole group synchronization lasted from 2s to a total of 12s ($M = 2.63$, $SD = 1.69$).

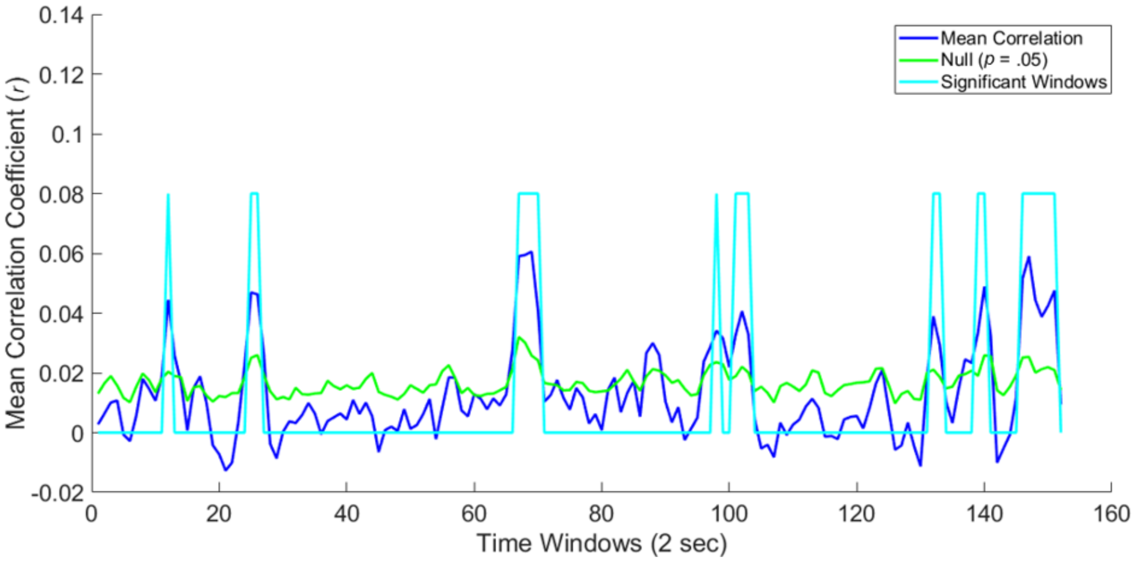

Figure 13. Mean ISC time course for healthy controls and Patient 3. The mean correlation coefficients (blue) plotted against the threshold for statistical significance (green), with windows of significant group-level ISC (turquoise) outlining peaks in inter-subject synchronization.

Moving forward, a time-resolved form of the global ISC was also calculated to index the periods in which Patient 3 was significantly correlated with healthy controls during the intact version of "*Taken*". The results of this analysis showed that Patient 3's neural activity was significantly synchronized to the rest of the group for 62 of the 152 time windows (40.79%) or for 2m 04s of the audio. The magnitude of Patient 3's ISC time course fell between -.096 ($p > .05$ FDR corrected) and .166 ($p < .05$ FDR corrected) and patient-to-group synchronization spanned from 2s to 18s ($M = 3.44$, $SD = 2.28$). For the controls, the number significant periods of individual-to-group synchronization ranged from 5 to 39 ($M = 19.20$, $SD = 8.38$) but all were significantly lower than what was observed for Patient 3, $\chi^2(1, N = 152) = 7.82$, $p = .005$ (test performed between Patient 3 and Participant 4 who ranked second for the number significant windows). The global ISC time course for Patient 3 is plotted relative to healthy controls in Figure 13 (top). Additionally, rather than dissect the similarities and differences between the global ISC time courses from 16 single subjects, the significant periods of ISC between Patient 3 and healthy controls were binarized and plotted as a kind of synchrony "barcode" in Figure 14 (middle). For comparison purposes, this binarized ISC for Participant 4 is also displayed in Figure 14 (bottom).

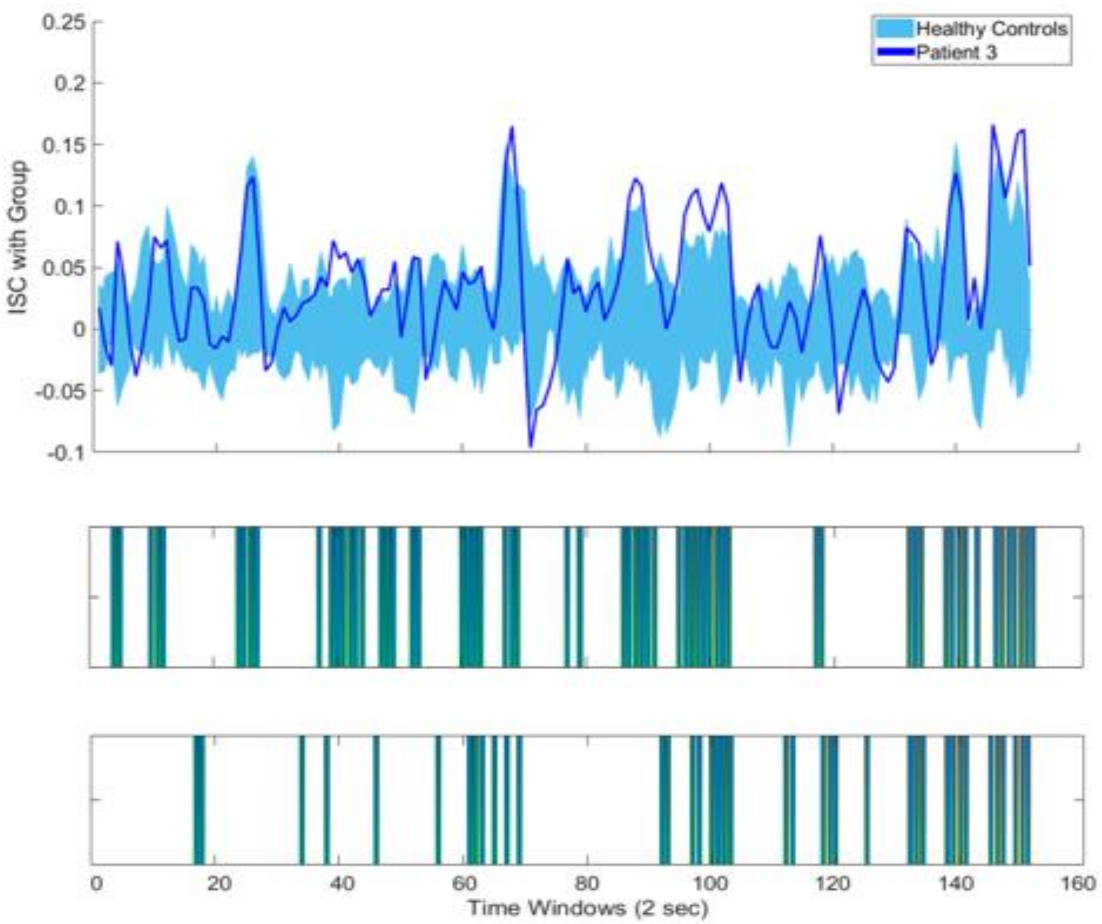

Figure 14. Time-resolved global ISC for Patient 3 and periods of significant synchronization. Top: Synchronization over time between Patient 3 (navy) and healthy controls (teal) during the intact stimulus condition. Middle: Dashes which represent time windows with significant patient-to-group synchrony. Bottom: Markers of significant participant-to-group synchronization for Participant 4.

Individual Assessments of Neural Synchronization between Patients with DOC and Healthy Controls: Patient Five

The rCA was again recalculated with *N* = 16 EEG data sets recorded from 15 healthy controls and Patient 5 (diagnosed as VS; CRS-R = 5) during the intact audio condition. The resulting component topography is presented in Figure 15a. Visually, the spatial configuration of this component was nearly identical to healthy controls' during the intact audio condition. This was confirmed by a dot product of 1.53 between the component vectors, denoting a substantial spatial similarity between the two, Furthermore, this component was mathematically closest to the top component in healthy controls (i.e., the most correlated between subjects) compared to any of the other 91 components generated from their EEG data. The spatial similarity between this and the scrambled component from healthy controls was correspondingly low, with a dot product = -.21, and likewise, low for the intact audio component found at the group-level in patients with DOC, dot product = 0.24 (Jackson & Sherratt, 2004).

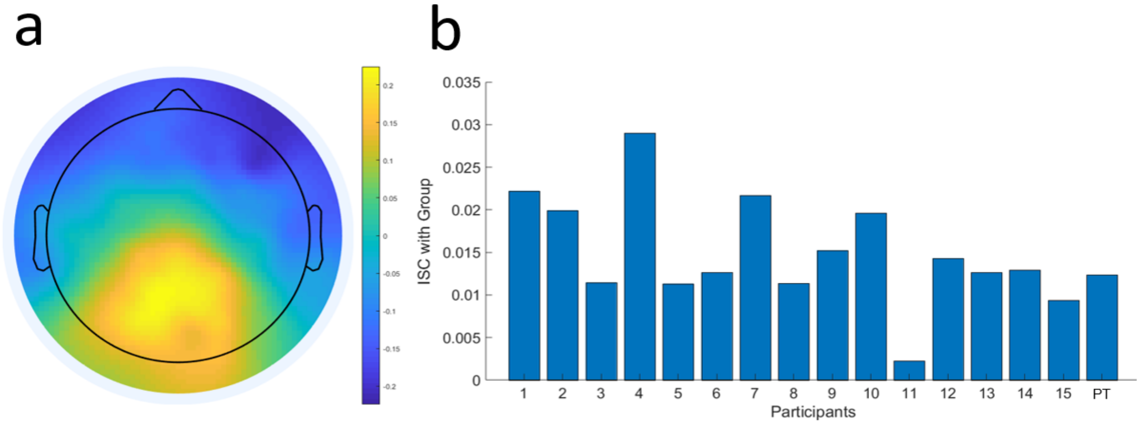

Figure 15. rCA component projection and global ISC for healthy controls and Patient 5 during the intact audio condition. a.) The topography which is maximally correlated between subjects in this sample. b.) Overall individual-to-group synchronization for Patient 5 (end) and healthy controls.

Overall group-level ISC are displayed in Figure 14b. Individual-to-group synchronization over the entire clip ranged from .002 to .029 ($M = .015$, $SD = .006$) with Patient 5 falling in the mid-range of healthy controls, ranking 10th in global ISC magnitude. The mean global ISC did not differ significantly from the intact audio condition, two sample $t(29) = 0.55$, $p = .58$, or for the scrambled audio condition in healthy controls, two sample $t(29) = -0.44$, $p = .66$. The group-averaged ISC was also calculated at 2s intervals over the entire narrative. The mean ISC time course, its significance thresholds, and windows of significant ISC are shown in Figure 16. Significant mean ISC was observed during 34 of the 152 time points (22.37%) in this sample which was a slight increase from healthy controls alone, $\chi^2(1, N = 152) = 0.89$, $p = .89$ and lasted from 2s to 10s ($M = 3.10$, $SD = 1.29$). Likewise, the number of time windows with significant neural synchronization was statistically greater than healthy controls' during the scrambled audio condition, $\chi^2(1, N = 152) = 5.13$, $p = .02$, and compared to the intact audio condition in the cohort of patients with DOC, $\chi^2(1, N = 152) = 22.49$, $p < .0001$. The magnitudes of the mean ISC ranged from -.015 ($p > .05$, FDR corrected) and .11 ($p < .05$, FDR corrected).

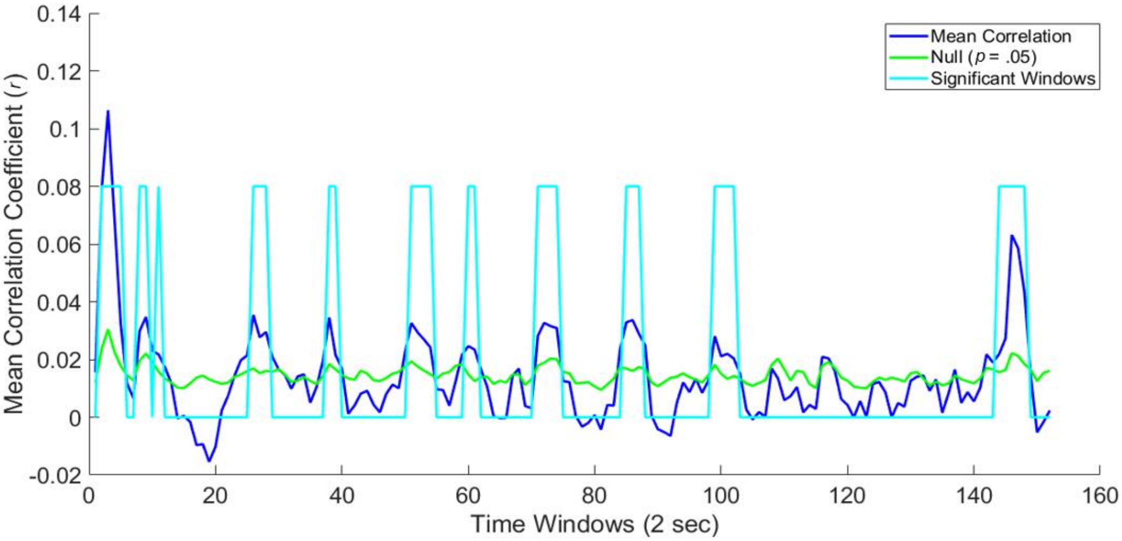

Figure 16. Mean ISC time course for Patient 5 and healthy controls during the intact audio condition. The averaged inter-subject correlations (blue) plotted against the correlation coefficients which correspond to the top 5% of a randomly sampled null distribution (green). Windows of significant ISC (turquoise) mark periods of whole-group synchrony.

The global ISC measure was recomputed using a sliding window to determine how frequently, and at which points in time, Patient 5 was significantly correlated with the healthy controls. Patient 5's neural activity was significantly synchronized to the group during 24 of the 152 time windows (15.79%) or for 48s during the intact presentation of "*Taken*" and spanned from 2s to 10s (*M* = 2.67, *SD* = 1.32). The magnitude of Patient 5's correlation with the group ranged from -.072 ($p > .05$ FDR corrected) to .108 ($p < .05$ FDR corrected). Comparatively, the number of periods of significant synchronization for each control participant ranged from 4 to 53 (*M* = 22.69, *SD* = 14.34). Patient 5 ranked 9th in the group for the total number of significant time windows and was synchronized with the group significantly more often than four of the healthy controls, $\chi^2(1, N = 152) = 7.63$, $p = .006$ but significantly less often than three, $\chi^2(1, N = 152) = 3.96$, $p = .048$ (contrasts performed between Patient 5 and Participant 14 who had the fourth-lowest count of significant windows and Participant 7 who had the third-highest). Patient 5's global ISC time course is plotted against the healthy controls' in Figure 17 (top) and her "barcode" of neural synchronization is presented in Figure 17 (middle), alongside that was observed for Participant 4 (bottom).

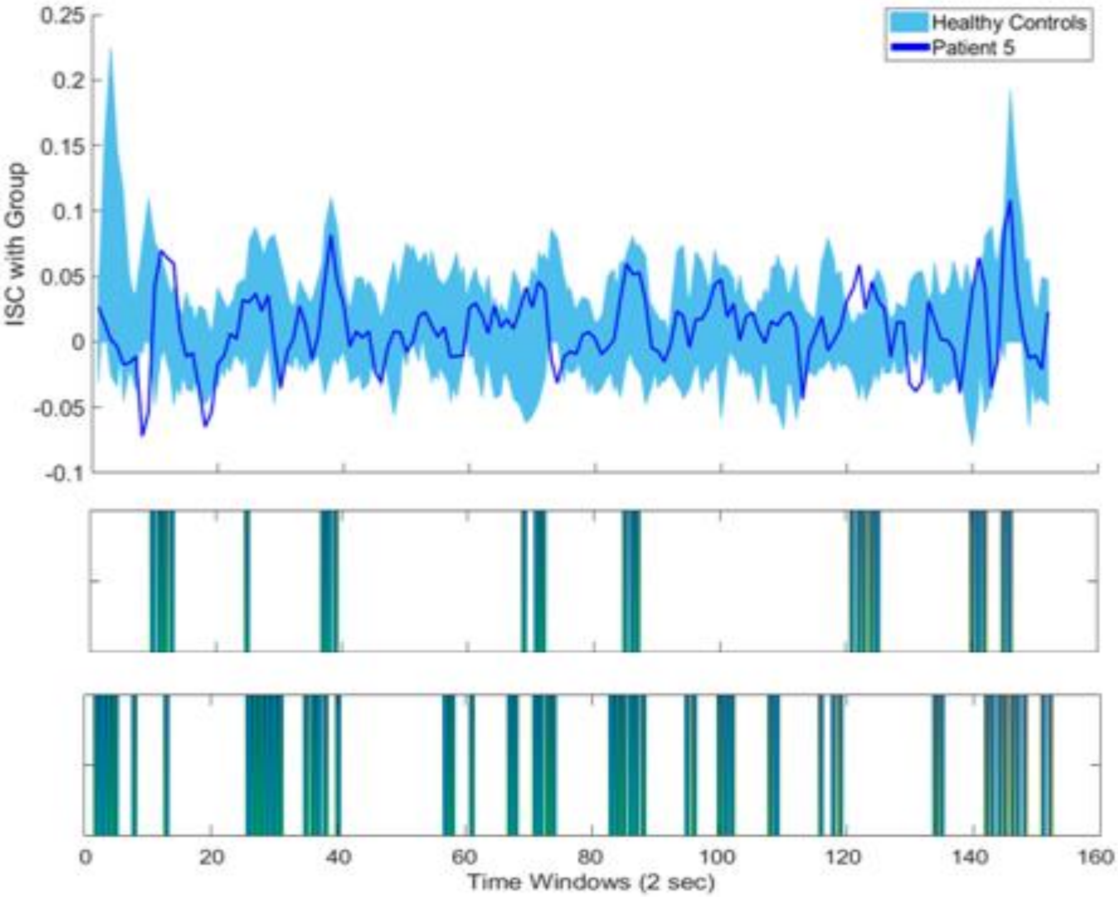

Figure 17. Time-resolved global ISC for Patient 5 and periods of significant synchronization. Top: Synchronization over time between Patient 5 (navy) and healthy controls (teal) during the intact stimulus condition. Middle: Dashes which represent time windows with significant patient-to-group synchrony. Bottom: Markers of significant participant-to-group synchronization for Participant 4.

Individual Assessments of Neural Synchronization between Patients with DOC and Healthy Controls: Patient Eight

Lastly, the rCA was run on $N = 16$ EEG data sets acquired from 15 healthy controls and Patient 8 (diagnosed as VS; CRS-R = 2) while they listened to the intact audio clip from "*Taken*". The correlated component topography is displayed in Figure 17a. The spatial distribution of electrode activity on this component showed an extensive, high-powered fronto-temporal positivity with a transition towards a moderate-to-high negativity over parietal/occipital regions of the scalp. This topography was spatially closest to the top component derived from healthy controls alone during the intact audio condition but the projection vectors trend in opposite directions, dot product = -1.07.

Likewise, this component showed a very low similarity to healthy controls' scrambled component, dot product = 0.08, or to the intact audio component computed for the patient group, dot product = -0.19 (Jackson & Sherratt, 2004).

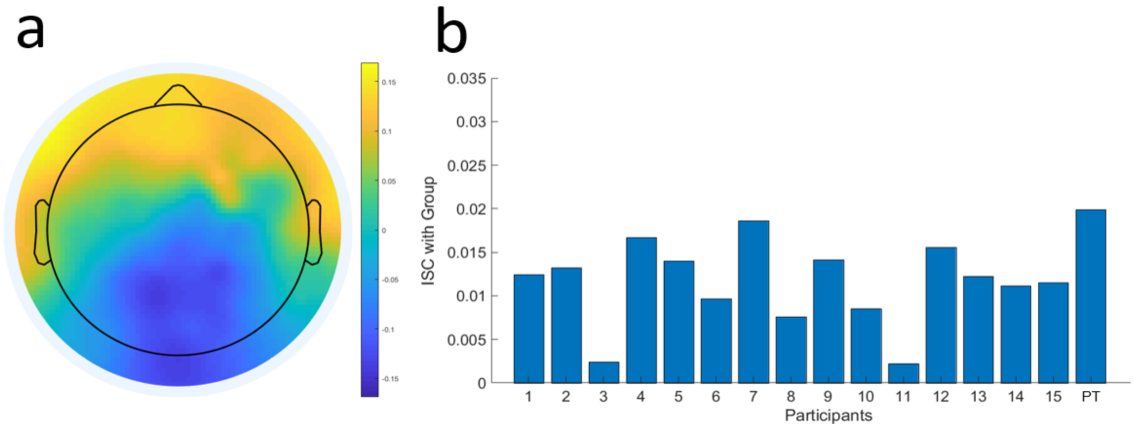

Figure 18. rCA component projection and global ISC for healthy controls and Patient 8 during the intact audio condition. a.) The topography which is maximally correlated between subjects in this sample. b.) Overall individual-to-group synchronization for Patient 8 (end) and healthy controls.

The global ISC for each participant in this sample, including Patient 8, is presented in Figure 17b. Group-level ISC fell between .002 and .020 (M = .012, SD = .005) and was, overall, significantly lower than the same condition in healthy controls, two sample $t(29) = 2.07$, $p = .04$. The average global ISC did not differ significantly from healthy controls in the scrambled audio condition, two sample $t(29) = 1.03$, $p = .03$. Patient 8's global ISC magnitude was the highest out of any of the participants in this sample. To track the changes in group-level synchronization over time, the mean ISC time course was also computed and is presented alongside its statistical thresholds and the periods of significant synchronization in Figure 19. Significant group-level ISC occurred in just 6 of the 152 time windows (3.95%), patient group during the intact audio condition, which was significantly lower than both the intact, $\chi^2(1, N = 152) = 21.35$, $p < .0001$, and scrambled audio conditions for healthy controls, $\chi^2(1, N = 152) = 9.56$, $p = .002$. Significant inter-subject synchronization lasted from 4s to 12s (M = 3.00, SD = 1.41). The magnitude of the average ISC ranged from -.011 ($p > .05$, FDR corrected) to .088 ($p < .05$, FDR corrected).

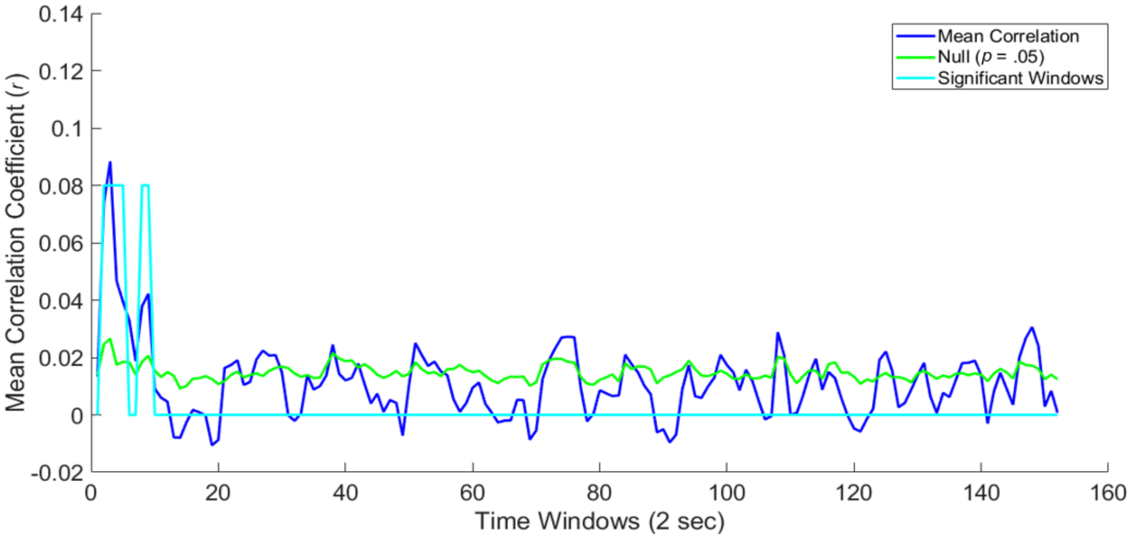

Figure 19. Mean ISC time course for Patient 8 and healthy controls during the intact audio condition. The mean inter-subject correlation (blue), significance thresholds at each time point (green), and windows of significant group-level ISC (turquoise).

Global ISC were recomputed in time using a sliding window to assess patient-to-group synchronization over the length of the intact audio. Patient 8 was significantly correlated with the rest of the healthy controls for 45 of the 152 time windows (29.61%) or for a total of 1m 30s, and last between 2 and 12s (*M* = 2.5, *SD* = 1.54). In healthy controls, for comparison, these number of periods of significant individual-to-group ISC ranged from 3 to 37 (*M* = 19.20, *SD* = 11.60). The magnitude of Patient 8's time course of global ISC ranged from -.068 ($p > .05$ FDR corrected) to .159 ($p > .05$ FDR corrected). Compared to the healthy controls, Patient 8 was synchronized with the rest of the group the most often, significantly more so than 11 of the 15 healthy controls tested here, $\chi^2(1, N = 152) = 6.6$, $p = .01$ (comparison made between Patient 8 and Participant 2 who had the sixth-highest number of significant time windows). The global ISC time course calculated for Patient 8 is presented relative to the healthy controls' in Figure 20 (top) and his "barcode" of synchronization is shown in Figure 120 (middle) with Participant 4's for comparison (bottom).

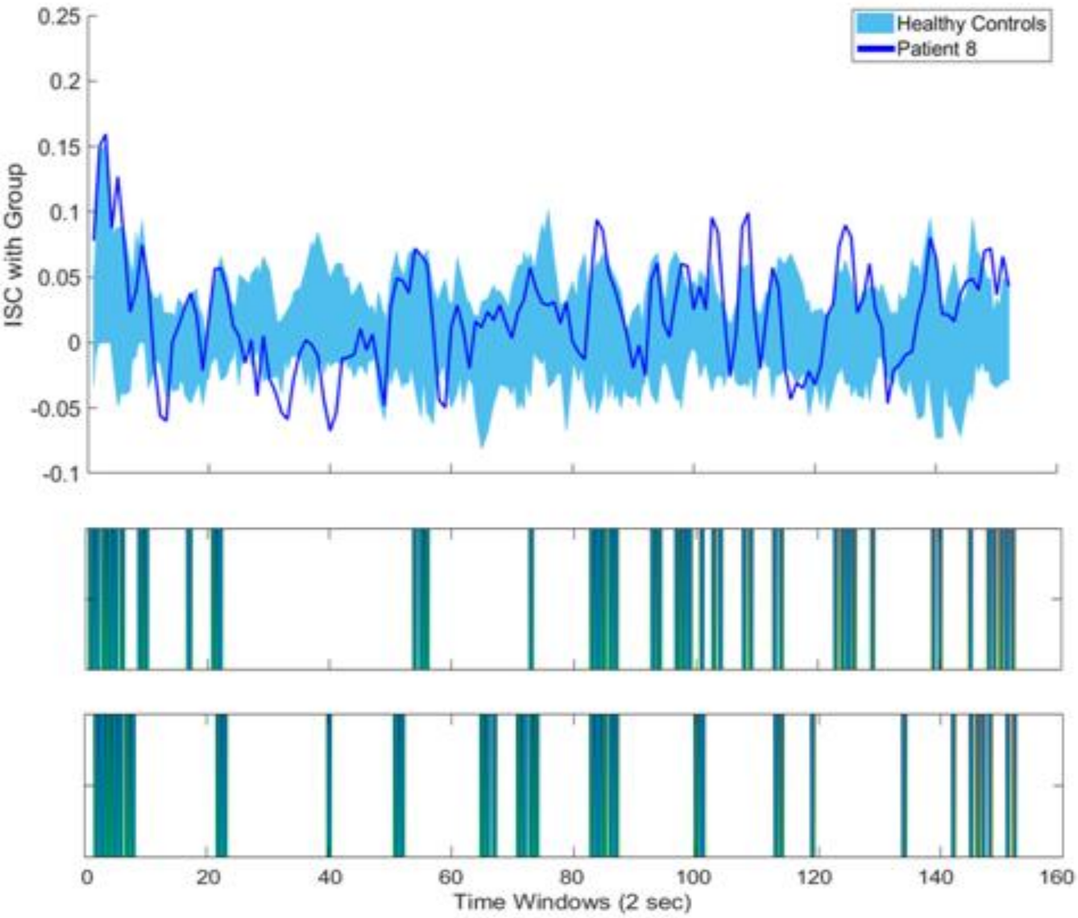

Figure 20. Time-resolved global ISC for Patient 8 and periods of significant synchronization. Top: Synchronization over time between Patient 8 (navy) and healthy controls (teal) during the intact stimulus condition. Middle: Dashes which represent time windows with significant patient-to-group synchrony. Bottom: Markers of significant participant-to-group synchronization for Participant 4.

Discussion

rCA was performed on the EEG data from a cohort of patients with DOC during the intact audio condition. Interestingly, the mean global ISC found for this cohort was significantly higher than healthy controls' in either audio condition. However, significant ISC was observed for only 4% of the clip from "*Taken*", and the mean the ISC time course were significantly lower overall than for healthy controls in either audio condition. What this suggests is that, while patients with DOC showed more within-group synchronization than healthy controls over the entire duration of the audio (see Chapter 4 for discussion), significant synchronization was infrequent and temporally unstructured during the "*Taken*" audio. What's more, the periods of significant inter-subject synchronization observed for the patient group occurred during particularly loud moments in the audio. The first two significant spikes in ISC in this group appeared to bracket a part of the stimulus that includes the sound of a phone ringing and a later section where loud rock music is being played in the background, and a following peak occurred shortly after one of the narrative's characters is kidnapped and can be heard screaming. This seems to suggest that these periods of significant ISC may be the result of an increase in the audio volume, or an attentional reorientation or startle responses elicited by this increase. Interestingly, the last time window with significant ISC in this group coincided with the climactic monologue from one of the main characters in the clip, though only for a brief time. This may be caused by increases in the perceptual properties (e.g., louder voices), or by an increase supramodal properties like suspense which increased engagement. To summarize, the group-level results from Experiment 2 found limited synchronization between patients, a high variability in patient-to-group ISC, and lower average ISC over the course of the audio clip. This is an intuitive result, given the varying etiologies, diagnoses, and stage of recovery of the patients sampled here, but it is also an important one; it established the neural dynamics of this group, providing another benchmark of synchronization with which to compare to individual patients with DOC.

Patient 3, a 51-year-old male diagnosed with locked in syndrome (CRS-R = 15; Kalmar & Giacino, 2005), was the first patient to be assessed on an individual basis using the rCA technique. Unlike the remainder of this cohort, Patient 3 is unequivocally aware and was therefore expected to respond to the "*Taken*" audio just as healthy controls and, indeed, this was largely supported by the results of this assessment. The rCA component topography computed for healthy controls and Patient 3 was spatially homologous to the one found for healthy controls alone in the intact audio condition (see Figure 8b and Figure 12a for comparison). On this component, the average global ISC across participants was not significantly different from either the intact audio condition or the scrambled condition in healthy participants and the same was true for the number of time points with significant group ISC in this sample. However, this is not to say that the group ISC was identical between samples.

At the group-level, the number of significant time windows did drop somewhat compared to the controls' in Experiment 1, potentially signifying a subtle reorganization of the spatial weights of the correlated component to incorporate Patient 3's neural response to the audio. While Patient 3 is undoubtedly conscious, serious brain injury leading to locked-in syndrome can have lasting effects on the architecture of EEG signals, which may have manifested in the reduction in the number of significant windows of group ISC reported here (Babiloni *et al.*, 2010; Gütling, Isenmann, & Wichmann, 1996). In fact, examining the group-level global ISC in this sample lends support to this notion, as Patient 3 produced a degree of individual-to-group level synchronization that fell within the range of all other participants, suggesting the top rCA component is well represented in this patient while listening to the "*Taken*" audio (see Figure 12b, end). In the same vein, the temporal order of the mean ISC time course generally resembled that of healthy controls', and the number of periods of significant ISC in this group was significantly higher than for the cohort of patients with DOC.

Patient 3's individual time-resolved synchronization with the group paralleled the relationship observed in the static global ISC measure; Patient 3 was reliably synchronized to the group as a whole more often than any individual healthy control participant, and was significantly so for close to half of the audio clip (40.79%; see Figure 14 top, middle). Despite the fact that this component was not identical to the one obtained from healthy controls in Experiment 1, its considerable similarity to it strengthens the likeness between them and Patient 3 during the task. This result is important because it is an additional validation that our analysis approach is sensitive to detecting similar patterns of brain activity in patients who have suffered serious brain injury, but are nonetheless objectively conscious. This is an encouraging result.

If rCA was sensitive enough to detect similar patterns of activity in a patient who we knew was conscious, could it do the same for a patient who shows no overt signs of awareness? To test this, we applied the rCA to EEG data acquired from Patient 5 while she listened to the intact version of "*Taken*". Patient 5 was a 48-year-old female who had remained behaviorally unresponsive after suffering serious traumatic brain injury more than two decades ago. Despite her vegetative state diagnosis (CRS-R = 5; Kalmar &

Giacino, 2005), previous fMRI studies found evidence of covert-command following in the scanner, as well as a limited capacity for communication through the willful modulation of her brain activity (Naci & Owen, 2013; Owen *et al*., 2006). However, during "*Bang! You're Dead*", Patient 5's BOLD activity was not significantly synchronized with healthy controls, though, speculatively, this may have been due to some form of injury-induced visual impairment. In the present study, the component found to maximize inter-subject correlations between the healthy controls and Patient 5 (see Figure 15a) remained largely unchanged from that observed for healthy controls in the same audio condition, as it had for Patient 3 (see Figure 8b). Likewise, and further echoing the similarity between the two samples, the average global ISC between participants did not differ significantly from either the intact or scrambled audio condition in healthy controls, which themselves were not statistically different from each other. This suggests that the neural response from Patient 5 during the "*Taken*" audio was sufficiently similar to healthy controls' as to preserve the overall group-level ISC. What's more, in addition to this similarity, Patient 5 fell within the top two-thirds of the range of individual-to-group synchronization calculated for healthy controls. We found the number of periods of significant group-level synchronization increased, though only slightly, relative to controls and was significantly higher than the scrambled audio condition in Experiment 1 and the patient group tested in Experiment 2. In sum, the results of the group-level analyses for this sample suggested that Patient 5's neural response to the "*Taken*" audio was similar-enough to healthy controls' as to not alter the component topography or the time course of mean ISC found in Experiment 1.

At an individual level, Patient 5 fell on the lower end of the distribution for group-level global ISC but was still, nevertheless, well within the range of healthy controls' (see Figure 15b, end). The same pattern also emerged in the time-resolved measure of global ISC. Patient 5 was synchronized with healthy controls for 15.79% of the audio, which was significantly more than four of the healthy controls in this sample (discussed in Chapter 4), with some periods of patient-to-group synchrony lasting up to 10s (see Figure 17 top, middle). Compared to the group-level mean ISC time course, Patient 5's synchrony with the group peaked at a number of key moments in the narrative, including the first instance of dialogue in the clip and the final climatic monologue delivered by one of the main characters.

Taken together, these findings suggest that, while she was on the low end of normal relative to healthy controls, Patient 5 processed at least some aspects of the narrative comparably to healthy controls. Indeed, the correlated component computed for this sample, including Patient 5, and the mean ISC time course were nearly identical to those observed for healthy participants. Moreover, the periods in which she was significantly correlated to the rest of the group frequently coincided with, not only those observed during the same audio condition in Experiment 1, but also with points in time that are significant to the development of the plot in "*Taken*". This latter result seems to underpin the contribution of executive processes in driving ISC in this sample and, potentially, in Patient 5.

Lastly, we analyzed the EEG data recorded from Patient 8 and the healthy controls during this task. Patient 8 was a 21-year-old male diagnosed as being in a vegetative state following traumatic brain injury (CRS-R = 2; Kalmar & Giacino, 2005). No previous imaging or electrophysiological data were available for Patient 8 prior to testing to provide a sketch of his neurological function but his behavioural responsivity during assessment with the CRS-R was decidedly low compared to other patients with DOC included in this study (Kalmar & Giacino, 2005). Visually, the component extracted from this sample was sharply dissimilar to all of the other components computed in this study (Figure 18a) Still, mathematically, this component showed a considerable likeness to healthy controls' during the intact version of "*Taken*", though the component vectors trended in opposite directions (see Figure 8b). The negative dot product value can be interpreted in two ways, though I will argue that, here, the latter is the more likely of the two. First, negative dot product values denote an inverse relationship between vectors which may be spatially analogous to one another. In the context of EEG, this could correspond to a pair of scalp topographies that are spatially identical but have inverted polarities, as is common in this neuroimaging modality (Jackson & Sherratt, 2004). Second, a large but negative dot product may also occur in cases where two vectors share a spatial configuration (i.e., the shape in which the electrode voltage is distributed across the scalp) but have truly opposing signals. Given the sizeable reduction in group-average ISC in this sample, it seems more probable that this component is altogether different from healthy controls'.

The group-level global ISC between healthy participants and Patient 8 was significantly lower than what was observed for healthy controls in the intact audio condition of Experiment 1, suggesting less individual-to-group ISC overall in this sample (see Figure 19). The reduction in group ISC is also mirrored in the mean ISC time course, which only saw 12s (6 time windows) of significant inter-subject synchronization over the entire length of "*Taken*" (3.95%). Additionally, the peaks in ISC occurred only during the first moments of the audio and could simply encapsulate the initial perceptual processing of the audio or an attentional orientation to it. This was statistically lower than the intact and scrambled audio conditions in healthy controls but is identical in number to the periods of significant ISC in the patient group. Linking back to the component topography calculated from this sample, it seems unlikely, given the dramatic reduction in mean ISC, that this component was merely an inverted version of healthy controls'. Rather, this new component appears to characterize a configuration of activity elicited during the audio that exists across many healthy controls but is most representative of Patient 8's neural processes.

Given these results, the individual synchronization observed between Patient 8 and the group over time is highly counterintuitive, especially considering the dearth of synchrony found at the group level. Over the duration of the audio, Patient 8 was significantly synchronized to healthy controls for a total of 1m 30s or for 45 time windows (29.61%), and lasted up to 12s (see Figure 20 top, middle). One explanation for this result, is that the component computed for this sample embodied a pattern of EEG activity that is ubiquitous across a significant number of healthy controls but is not involved to any large degree in the processing of the "*Taken*" narrative. The contrast between the group and individual level analyses suggests exactly this. By virtue of its roots in PCA, the rCA identifies numerous patterns of correlated electrode activity, some of which are surely separate from the executive processes involved in narrative processing (Dmochowski *et al.*, 2012). These may include the neural underpinnings of basic physiological processes, either stable or transient cognitive states, or potentially, high powered response to a discrete event in a stimulus such as a startle response to the phone ringing at the beginning of "*Taken*" (Fingelkurts *et al*., 2012; Lehmann & Michel, 2011). While its true source cannot be determined with certainty here, the data indicate that it was not a driving force of ISC during this task, and that it was maximally correlated between subjects only as a result of adding the EEG data from Patient 8.

When combined, the results from the individual assessment of Patient 8 provided little evidence of his residual executive processing capabilities. While a brief instance of whole-group synchronization was observed in this sample, its occurrence at the initial onset of the stimulus casts doubt on its relationship to the plot of the audio clip. Likewise, the significant reduction in group-level global ISC compared to the healthy controls suggests that this component was not representative of the neural activity typically involved in processing "*Taken*". At an individual level, however, Patient 8's synchronization with the group was both widespread and relatively long-lasting; he was significantly synchronized with the healthy controls for nearly one-third of the audio and this synchrony lasted up to 12s. Despite this, the component topography computed for Patient 8 showed an opposing pattern of activity to the one that has been consistently observed during the intact audio condition (i.e., for healthy controls, Patient 3, and Patient 5) and, as I have argued, likely does not reflect the same neural processes associated with narrative processing in this task. Of course, this should not be taken to suggest that this patient lacks awareness but rather that awareness cannot be established with certainty using the protocol presented here.

The individual patient assessments performed in the current study found a wide range of synchronization patterns during the "*Taken*" audio. First, the neural response from Patient 3 struck the best balance between maintaining significant group-level synchronization over the course of the audio and showing frequent and prolonged individual synchronization with the group. Indeed, despite a minor decrease, neither the mean ISC time course, nor global ISC with Patient 3 were statistically different from the healthy group, and he was significantly synchronized with controls for nearly half of the audio. While we know definitively that Patient 3 was processing the audio in the same manner as healthy controls, these data would support a similar conclusion. The results from Patient 5, however, are less clear, and show the opposite pattern. At the group level, Patient 5's neural activity appeared to reinforce the mean ISC time course, resulting in an additional window of significant synchronization. Likewise, the global ISC in this sample was not significantly different from controls'. Individually, though, Patient 5 was only sparsely synchronized with the group, albeit more-so than some healthy controls (discussed above) but the time points that she was largely coincided with moments that were relevant to the development of the narrative. This seems to suggest that, while somewhat infrequently, Patient 5's neural response to the "*Taken*" audio closely resembled healthy controls, providing evidence that she processed parts of the narrative in a way that would not be expected given her vegetative state diagnosis. Finally, the patterns of neural activity observed from Patient 8 were the most dissimilar to healthy controls among the patients assessed in this study. With his data included alongside healthy controls', the global ISC in this sample was significantly lower than in the control group, and the mean ISC time course lost all but six of its significant time windows, identical in number to the patient group. On an individual level, however, Patient 8 showed a level of synchronization with the group that was analogous to Patient 3, and far greater than Patient 5. However, as discussed previously, this synchronization occurred on a component that was markedly different to those observed in healthy controls, as well as in each patient, and likely was not a configuration of neural activity that was primarily involved in processing the narrative.

In summary, the results from Experiment 2 presented in this chapter provide good evidence to support using this method to detect executive processing, as a proxy measure of awareness, in patients with DOC. First, group-level analyses of the cohort of patients included in this study demonstrated that rCA and the follow-up analysis procedures presented here are robust to coincident patterns of neural activity unrelated to the task. The component computed for patients with DOC was nearly orthogonal to the intact and scrambled components found in healthy controls and, despite it being maximally correlated between patients, only resulted in significant synchrony during less than 4% of the audio clip. Considering the heterogeneity of diagnoses and abilities of the patients in this study, this is a fitting result. Importantly, individual assessments also established the ability of the rCA to index periods of significant neural synchronization with healthy controls on a per-patient basis. By combining the results obtained across each analysis, I was able to differentiate between two patients, one who we know is fully aware and one diagnosed as being in a vegetative state, on the basis of the similarity of their component topographies relative to healthy controls, as well as the number of periods in which they were significantly synchronized with the group over the course audio. However, interpreting the results from Patient 8 was less straightforward. Although I have argued that, given the available data, Patient 8’s neural response to “*Taken*” likely reflected neural processes that were unrelated to processing the audio, this cannot be fully confirmed here. In the following chapter, I will provide an overview of the results from both experiments conducted in this study, as well as address some of the remaining questions surrounding them. Additionally, I will discuss some of the limitations of the current study and its analysis procedures and provide an outline of possible future directions for this line of research.

Chapter 4: General Discussion

Summary of Findings

Over the course of two experiments, I demonstrated the feasibility of assessing executive processing in patients with DOC at the bedside using EEG. The transition from active, task-based assessments of awareness to more naturalistic paradigms was motivated by a desire to reduce the impact of testing on patients. Naturalistic paradigms, through their use of engaging movies or narratives, capture and sustain attention more easily than previous task designs, and do not require any form of response from the patient (Hasson *et al*., 2004; Naci *et al*., 2014, 2015). One of the major goals of the present study was to streamline this process even further by constructing a protocol built around these naturalistic experimental procedures that can also be implemented in relatively low-cost, portable neuroimaging equipment like EEG. This is an important endeavor because, to date, this line of work has almost exclusively been done using fMRI, which is not an ideal clinical tool. In order to achieve my goals, I have developed a bedside tool to assess awareness that is maximally conducive for patients with DOC that can also be used to cover the gaps left by the practical and technical limitations of fMRI.

To extend the analysis procedures using naturalistic paradigms with fMRI, I chose to use a novel EEG method developed by Dmochowski *et al*. (2012) to measure inter-subject neural synchronization, based on correlation component analysis (rCA), in healthy participants. This rCA capitalizes on the statistical foundations of PCA but extracts components that are maximally correlated between participants to track synchrony over the course of a given naturalistic stimulus (Dmochowski *et al*., 2012). My study is the first of its kind to investigate neural synchronization as a proxy measure of executive processing in patients with DOC using rCA during naturalistic auditory stimulation.

To establish a viable mechanism for detecting executive processing in patients, I first tested the protocol in healthy controls in Experiment 1. Participants listened to an intact and a scrambled version of a suspenseful audio clip from the movie "*Taken*" while their neural activity was recorded using EEG. The results of this experiment showed that the rCA could functionally differentiate the group-level neural response elicited by the two audio conditions based on the degree of inter-subject synchronization observed in each. Consistent with previous findings, the degree of ISC was significantly reduced for the scrambled audio compared to the intact version of the stimulus (Dmochowski *et al*., 2012; Ki *et al*., 2016; Naci *et al*., 2014, 2015).

I extended this protocol to assess executive processing in a cohort of patients with DOC in Experiment 2. At the group level, I found that, interestingly, global inter-subject synchronization was significantly higher for the group of patients than for healthy controls over the entire duration of the audio. Nevertheless, this did not translate into significant group-level synchronization over time; the number of two-second time windows with significant synchrony for the patient group was significantly lower than either of the audio conditions in healthy controls, highlighting one of the advantages of using temporally resolved measures of inter-subject synchronization. At the individual subject level, however, two patients, Patient 3 who was diagnosed with locked-in syndrome and Patient 5 who fit the behavioural criteria for being in a vegetative state, exhibited patterns of neural activity that closely resembled what was observed in healthy controls and were significantly synchronized with the healthy controls at meaningful points during the audio (i.e., periods that were important to the development of the plot). Additionally, Patient 8 who also met the criteria for a vegetative state diagnosis was significantly synchronized with healthy controls over a large portion of the task. However, the component observed for Patient 8 was markedly dissimilar to the one that was repeatedly produced by healthy controls.

The utility of recording EEG while patients listened to a viable clinical tool was further supported by establishing specificity based on the results found in Experiment 2. Both Patient 3 and Patient 5 were significantly correlated with healthy controls on a component that largely matched their own during the same audio condition, but Patient 3 was considerably more so than Patient 5. This is an important finding, given that Patient 3 is verifiably conscious, whereas there is only modest evidence to suggest that Patient 5 may retain a degree of covert awareness – that is, she can follow commands. Still, her neural response to the “*Taken*” audio fell within the range of healthy controls and was significantly synchronized with the group for 16% of the audio, which was more than expected given her behavioural diagnosis (Kalmar & Giacino, 2005). In contrast, Patient 8 produced a response to the audio that was uniquely dissimilar to healthy controls'. The component topography generated with Patient 8 was the inverse of the one found in the control group, Patient 3, and Patient 5. This resulted in a significant reduction of the number of windows with significant mean ISC at the group level, to the point of being as low as the number observed for the patient group. What this suggests is that, despite being maximally correlated across participants, the component did not represent a pattern of neural activity that was chiefly involved in processing "*Taken*". Individually, Patient 8 was frequently synchronized with the group, and more so than many other participants in this sample, but on a component that was vastly different from healthy controls'.

The results pertaining to Patient 8 raise one of the more interesting findings of this study. Namely, that Patient 5 was significantly more correlated to the group than four of the healthy controls. From an electrophysiological perspective, this result may stem from reduced differentiation of functional states of the brain in patients with DOC. Fingelkurts *et al*. (2012) found that patients who remain behaviourally non-responsive following severe brain injury have a significantly diminished number of EEG microstates, that is, the repertoire of quasi-stable states of the brain underlying resting states and certain cognitive functions, compared to healthy individuals (Lehmann & Michel, 2011). Additionally, the frequency with which patients with DOC transition between these states is also significantly reduced (Fingelkurts *et al*., 2012). What this could suggest is that, if the narrative of "*Taken*" loads on a configuration of neural activity that remains present in patients with DOC, as appeared to be the case in Patient 3 and Patient 5 in this study, it may be more temporally stable than in some healthy controls.

On a related, but less technical point, the greater synchrony observed for Patient 5 may reflect the inherent variability in the way we process naturalistic stimuli like movies and stories. The rCA extracts components that are maximally correlated in the group but, as I have presented here, assessments of individual-to-group synchronization result in a distribution of similarities across participants. A pattern of neural activity that best captures group-level synchrony may not be perfectly representative of the response from each subject during the audio and, even if it is, it might be one that occurs less frequently for some participants. To the former, it is possible that some people simply processed the narrative in a different way; perhaps one or more of the participants in this study had seen or heard this clip from "*Taken*" before and, as a result, found it less suspenseful than others who have not (Dmochowski *et al*. 2012). It could also be the case that some participants are naturally more or less affected by suspenseful movies. To the latter point above, participants who experienced periodic shifts or lapses in attention, or those who were mind wandering during the clip would likely show less group synchrony than those who were fully engaged in it. These individual differences may explain, in part, why Patient 5 was more correlated with the group than some healthy controls. Nevertheless, one of the stated goals of Experiment 1 was to establish a distribution of synchronization in healthy controls to use as a benchmark of executive processing during the intact version of "*Taken*". Although the distribution of synchrony observed here was wider than initially predicted, and resulted in an initially counter-intuitive result for Patient 5, it still provided a valuable metric for group-level and individual patient assessments in Experiment 2 and may remain as such for future investigations.

Study Limitations

Despite its successes, the rCA is limited with respect to the sources of the correlated components found in this study. Unlike fMRI, components observed at the scalp level in EEG do not necessarily correspond to specific spatial locations in the brain, and may in fact represent an infinite number of different configurations of neuronal activity (Michel *et al*., 2004). With the exception of a small number of topographies found to represent well documented ERP waveforms like the P300, it is difficult to ascribe a singular component to any one cognitive function, no less the constellation of functions that support sustained executive processing (Dmochowski, Ki, Deguzman, Sajda, & Parra, 2016; Dmochowski *et al*., 2012). Likewise, the foundation of rCA in an exploratory statistical analysis procedure like PCA results in generating a number of correlated components equal to the number of recording sites (i.e., electrodes) used to acquire the data (Dmochowski *et al*., 2012; Shlens, 2009). This may result in a fractionation of specific cognitive processes across multiple topographies and time courses, further obscuring their true neural underpinnings (Dmochowski *et al*., 2016).

In the pilot study of this analysis, Dmochowski *et al*. (2012) sought to address this by estimating the neural generators of their correlated components using a source-localization algorithm. They projected the component topographies obtained from "*Bang! You're Dead*" onto a low-resolution cortical model and found activity localized to the cingulate cortex, parahippocampal gyri, and areas of the parietal cortex. The parallels between these findings and those of Naci *et al*. (2015), show promise, but more work is required before definitive claims can be made regarding the neural sources of these components or the corresponding cognitive functions which underlie them. A future direction for this line of research, and one that is already underway, is to model the time courses of the rCA components in source-space in addition to estimating their locations, something that was not performed by Dmochowski *et al*., to more closely compare to the available fMRI data (Custo, Vulliemoz, Grouiller, Van De Ville, & Michel, 2014).

A second limitation of this study relates to the need for further validation of the rCA procedure. To date, only one other lab has used rCA to track inter-subject synchronization during naturalistic stimulation in healthy controls. Although their findings are consistent and show a considerable reliability across studies, it remains to be seen whether this is the result of having captured the true electrophysiological signatures of engagement and executive processing or if it is a by-product of the analysis itself. In one study, Cohen and Parra (2016) applied the rCA to EEG data recorded during bimodal (audiovisual) and unimodal (audio only) stimulus conditions. While their main findings were that ISC was significantly lower for unimodal stimuli, the resulting component projection from this condition bared a striking resemblance, not only to the bimodal component reported in the study, but also to those reported in previously during audiovisual stimulus conditions (Dmochowski *et al*., 2014, 2012). Given what we know about the differences between unimodal and bimodal stimulus processing at the neural level, this is a surprising result. Additionally, although the results from the current study show high internal validity, the component topography we observed during the "*Taken*" audio was not identical to the one reported by Cohen and Parra. It is certainly possible that both components reflect different neural configurations of engagement and executive processing, as this may be distributed across multiple rCA components (mentioned previously), but further work is required to establish this. Going forward, relating objective measures of stimulus engagement to the results from the rCA could also help to validate this procedure. This could be accomplished by regressing the ISC data onto a variation of the SART used by Naci *et al*. (2014), analyzing eye-movement data during an audiovisual version of this task, or by collecting other behavioural data from online sources to index periods of high and low engagement with the audio clip.

Lastly, only the top components extracted by the rCA in each condition, that is, the ones which maximize inter-subject correlations, were selected further for analysis. I argued that the two audio conditions were differentiated by their respective components on the basis of their involvement of executive processes (Naci *et al*., 2014, 2015). I also made the case that these executive processes were the driving force behind the differences observed between healthy controls and patients with DOC during the intact audio condition. However, in fMRI, Naci *et al*. (2014, 2015) found that peak inter-subject synchronization occurs in primary and associated sensory networks, such as the visual and auditory cortices, rather than the fronto-partietal executive network. Although it is possible that the rCA components which were the most synchronized between participants encapsulate more sensory than executive processes, I will argue that the EEG components identified here reflect, at least, an additive combination of both.

The correlated component found during the scrambled audio condition was intended to serve as a control, measuring primarily sensory-driven synchronization in healthy participants. The time course of significant ISC in this condition could then be partitioned as relating to the physical properties of the audio, rather than to the plot of the narrative in the intact audio condition. In this way, periods of synchronization above what was observed during the scrambled audio condition, both in terms of ISC magnitude and frequency of significant synchrony, must, therefore, be due to extra-sensory properties of the intact narrative, including that of discernable speech (discussed in Chapter 2) and, importantly, its plot. Indeed, this is precisely what was seen in the results of Experiment 1. In addition to the increase in time windows with significant ISC in the intact audio condition, many of which appearing to relate to critical moments in the narrative, the magnitudes of the inter-subject correlations increased overall, as well as during periods of significant ISC during the scrambled audio condition. This suggests that, while the rCA likely captured some elements of sensory processing, the correlated components observed during the intact stimulus condition are composed of additional neural activity involved with narrative processing. As well as finding components that underlying executive processes, future studies should also search for those that are purely sensory, for instance, by looking to correlate the component time courses for each condition with the auditory envelope from the intact and scrambled versions of "*Taken*". This way, evaluations about the patients sensory and executive processing abilities can be made in a hierarchical fashion; sensory components would establish intact auditory (or visual) perception, providing the foundation from which to scaffold the components of executive processing.

Significance and Future Directions

In this study, I evaluated the utility of using a naturalistic EEG-based assessment of executive processing as a proxy measure of awareness in patients with DOC. In healthy controls, I demonstrated that a novel EEG analysis technique could discriminate the neural responses elicited by a suspenseful auditory narrative and a scrambled control condition using inter-subject synchronization alone. I then extended this paradigm to test a cohort of patients with DOC. At the group level, the results more closely resembled those found during the scrambled audio condition in healthy controls, signifying little inter-subject synchronization in this group. At an individual level, however, this measure of inter-subject synchronization was able to identify one patient with locked-in syndrome based on the high degree similarity between their neural response, both spatially across the scalp and over time, and that of healthy controls. Additionally, two behaviourally unresponsive patients with DOC were also evaluated in the present study. Although the results for one were largely inconsistent with what was seen previously for healthy controls, as well as for the locked-in patient, I found limited but significant synchronization between healthy controls and this second patient during the intact presentation of the "*Taken*" audio. Previous studies have shown evidence that this patient may be partly covertly aware and the results of this study support these findings.

I have shown that rCA, coupled with the task-free paradigms using EEG is a suitable means to assess executive processing in patients with DOC. EEG is a low-cost, portable, and low-impact neuroimaging technique which can be applied rapidly and at a patient's bedside. These attributes afford frequent and repeated testing sessions which could then be used to profile the day-to-day progression of a patient's neural responsivity to naturalistic stimuli. To this point, the paradigm and analyses presented here may also be useful in tracking recovery in patients with acute brain injury or to measure variations in neural activity associated with changes in a patient's medical management (e.g., after beginning or ceasing a medication regimen). Going forward, this paradigm may provide a powerful tool for the bedside testing of patients with DOC.

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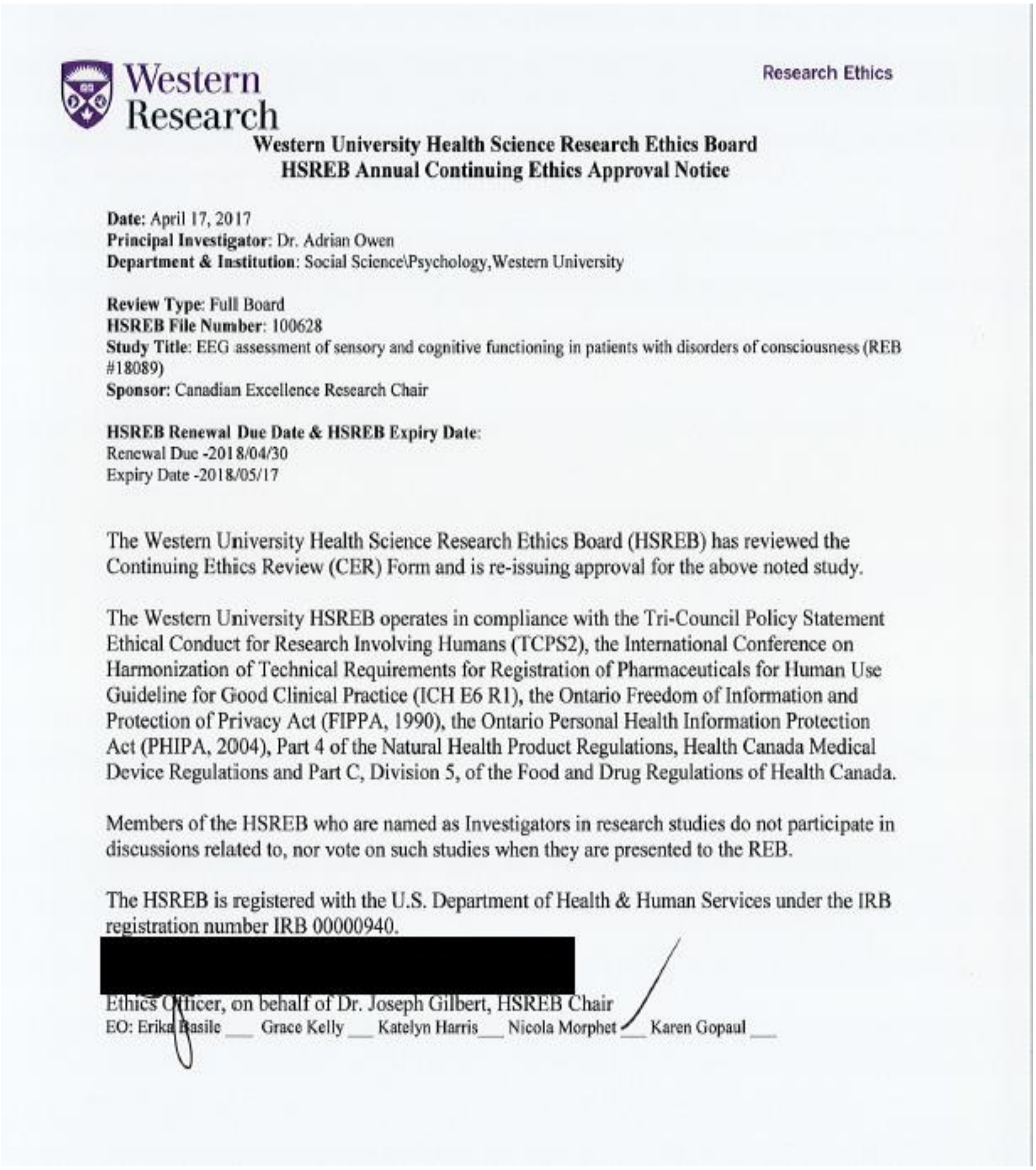
Appendix A - Ethics



Western Research

Research Ethics

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

Date: April 17, 2017
Principal Investigator: Dr. Adrian Owen
Department & Institution: Social Science\Psychology,Western University

Review Type: Full Board
HSREB File Number: 100628
Study Title: EEG assessment of sensory and cognitive functioning in patients with disorders of consciousness (REB #18089)
Sponsor: Canadian Excellence Research Chair

HSREB Renewal Due Date & HSREB Expiry Date:
Renewal Due -2018/04/30
Expiry Date -2018/05/17

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 00000940.

[redacted]

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair
EO: Erika Basile ___ Grace Kelly ___ Katelyn Harris ___ Nicola Morphet ✓ Karen Gopaul ___

Appendix B - Group-level Results from the Noise Control Condition

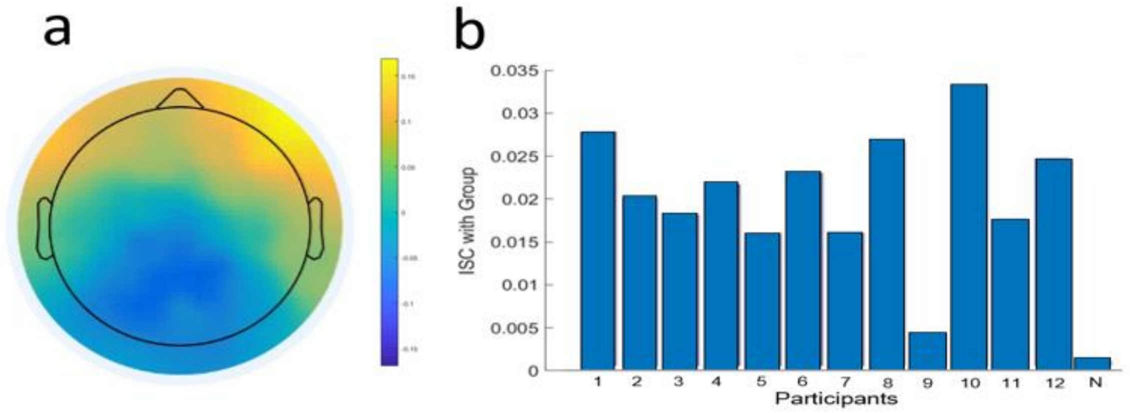


Figure 21. rCA component projection and global ISC for the noise control condition. a.) The spatial topography of electrode activity which maximized Pearson's correlation between *N* = 12 healthy participants and one data set ("N") generated from pure noise. b.) The magnitude of individual-to-group ISC across participants for the duration of the noise condition.

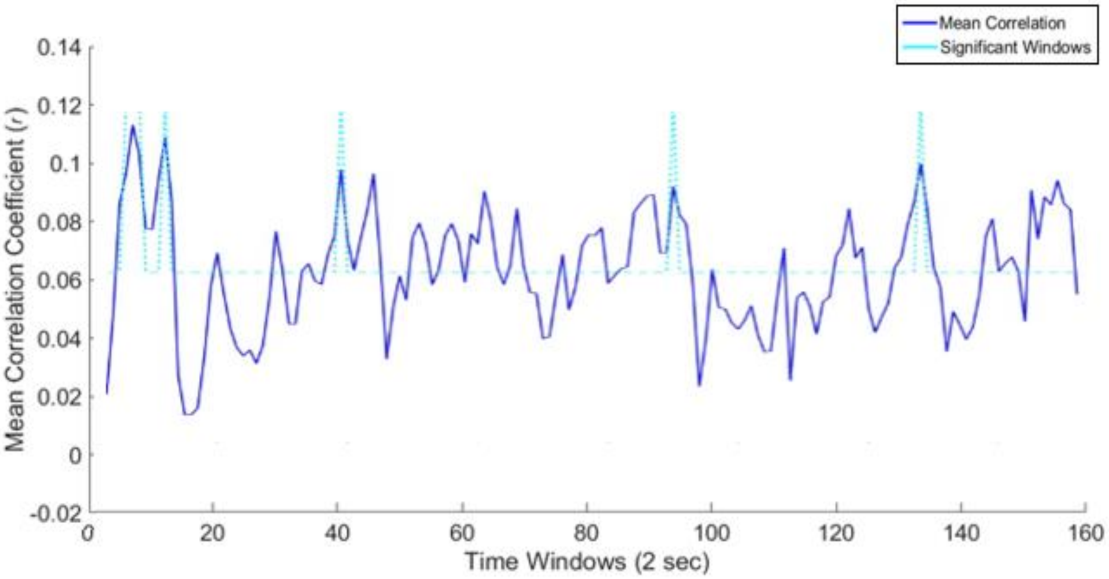


Figure 22. Mean ISC time course for the healthy controls and one data set of pure noise. Magnitude of the average inter-subject correlations (blue) and windows of significant inter-subject synchronization (turquoise) outlining peaks in inter-subject synchronization.

Curriculum Vitae

Geoffrey Laforge

EDUCATION

Sept. 2017 - Present	Ph.D. Psychology - The University of Western Ontario Expected Aug. 2021 Supervisor: Adrian Owen
Sept. 2015 - Aug. 2017	M.Sc. Psychology - The University of Western Ontario Supervisor: Adrian Owen **Thesis title**: Identifying Electrophysiological Components of Covert Awareness in Patients with Disorders of Consciousness
Sept. 2011 - May 2015	B.Sc. Psychology - Trent University Supervisor: Ben Bauer **Thesis title**: Crowd(un)sourcing: The Effect of Diffuse Visual Attention on Target Orientation Discrimination

RESEARCH

Aug. 2017	Ben Bauer. Perceptual Averaging of Line Length: Effects of Concurrent Digit Memory Load. *Attention, Perception, and Psychophysics,* 1. *Awknowledgement*.
Sept. 2015 - Aug. 2017	Owen Lab - The University of Western Ontario - Electroencephalography, Disorders of consciousness
Sept. 2014 - April 2015	Language and Cognition Lab - Trent University - Developmental executive function, Mind-reading
Sept. 2013 - Jan. 2014	Vision and Cognition Lab Assistant - Trent University - Early visual processing, Attention, Psychophysics

TEACHING/PROFESSIONAL EXPERIENCE

Sept. 2017 - April 2018	**Head Teaching Assistant** Research Methods and Statistical Analysis in Psychology - The University of Western Ontario
Sept. 2016 - April 2017	**Graduate Teaching Assistant - Lecturer** Research Methods and Statistical Analysis in Psychology - The University of Western Ontario

Sept. 2015 - April 2016	**Graduate Teaching Assistant - Lecturer** Research Methods and Statistical Analysis in Psychology - The University of Western Ontario
April 2015	**Essay Marker** Introduction to Philosophy of Mind - Trent University
Oct. 2013 - Feb. 2015	**Exam Marker** Introduction to Philosophy of Mind - Trent University

CONFERENCES

February, 2017	Lower Ontario Visionary Establishment Niagara Falls, ON Identifying Electrophysiological Indices of Covert Awareness in Patients with Disorders of Consciousness. *Poster*
May, 2015	Attention and Conscious Perception Toronto, ON.
July, 2014	Canadian Society for Brain, Behaviour, and Cognitive Science. Toronto, ON. “Better When Loaded, on Average”, Ben Bauer. *Acknowledgement*

EXTRACURRICULARS

Sept. 2013 - April 2014	**Academic Peer Mentor -** Trent University Introduction to Statistics, Cognitive Psychology, Physiological Psychology
April 2013 - April 2014	**Student Director of Psychology -** Trent University Trent Oshawa Student Association
Sept. 2013 - April 2015	**Club Vice President -** Trent University Trent Oshawa Psychology Association