Movies on the Mind: Using Naturalistic Stimuli to Assess Perception, Cognition, and Awareness in Patients with Disorders of Consciousness

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Psychology

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Abstract

Standardized behavioural assessments of awareness remain the gold standard for patients with disorders of consciousness (DOC) and inform diagnosis, prognosis, and medical decision-making. However, recent neuroimaging research has identified a small but significant number of DOC patients who retain perceptual and cognitive abilities not evidenced by their behaviour. Therefore, it is imperative to develop assessment techniques to identify and characterize the conscious experiences of patients with DOC.

This thesis presents a novel movie-based electroencephalographic (EEG) assessment of perceptual and cognitive function in DOC patients. In Chapter 2, we calculated EEG inter-subject correlations (ISCs) in healthy controls and DOC patients to index higher-order “executive” processing of two types of movie stimuli (audio-visual, audio-only). Contrary to their behavioural diagnosis, 25% and 30% of patients showed preserved perceptual and cognitive abilities necessary to process the audio-visual and auditory movies, respectively. In Chapter 3, we determined whether a translated version of the auditory movie could be used to assess French-speaking populations of DOC patients. Here, two groups of healthy controls (English and French-speaking) showed comparable degrees of ISCs that occurred at roughly the same timepoints across languages. In Chapter 4, we explored the prognostic utility of ISCs, functional connectivity, and source localized EEG activity in a cohort of patients with severe acute brain injury. ISCs and functional connectivity, but not source localized activity, were marginally predictive of outcomes after severe brain injury. Over three studies, we developed and validated a novel EEG assessment of perceptual and cognitive function in DOC patients, demonstrated its potential application in English and French populations, and established the feasibility of this assessment in acutely brain-injured patients.
Keywords

Disorders of consciousness, naturalistic stimuli, electroencephalography, severe brain injury, components analysis, anesthesia.
Summary for Lay Audience

Disorders of consciousness (DOC) are a class of neurological disorders that can result from severe brain injury. Patients with DOC exhibit minimal behavioural evidence that they are aware of themselves or their environment; they may appear to be awake but fail to respond to stimulation or verbal command. However, DOC are diagnosed solely on the basis of observable behaviour, which may be impaired in patients with severe brain injury. Recent neuroimaging research has identified a small but significant number of DOC patients who show neural evidence of conscious awareness, despite remaining behaviourally non-responsive. One method to uncover the neural correlates of awareness in DOC patients is to use movie stimuli and track patients’ neural responses to elements of the story like its suspense, which cannot be processed unconsciously. This thesis presents a novel movie-based electroencephalographic (EEG) assessment of residual awareness in patients with DOC. In Chapter 2, we calculated EEG inter-subject correlations (ISCs) between healthy controls and patients with DOC to compare the similarity of their neural responses during two movie types (audio-visual, audio only). Overall, 25% and 30% of patients produced neural activity that closely resembled healthy controls—suggesting a comparable degree of narrative processing—during the audio-visual and audio movie, respectively. In Chapter 3, we compared EEG activity across English and French-speaking healthy controls to determine whether a translated (to French) version of the auditory movie assessment was suitable for French-speaking DOC patients. Here, both groups produced comparable degrees of ISCs that occurred at roughly the same time points, thereby validating this assessment for French-speaking populations of DOC patients. In Chapter 4, we explored whether the auditory movie could help predict recovery from recent serious brain injury. We found that ISCs and EEG functional connectivity were marginally associated with survival. Over three studies, we developed and validated a novel EEG assessment of awareness in DOC patients, demonstrated its potential application in English and French populations, and established the feasibility of this assessment in recently brain-injured patients.
Co-authorship Statement

Geoffrey Laforge, Laura Gonzalez-Lara, Natalia Incio Serra, Stefanie Blain-Moraes, Bobby Stojanoski, Adrian M. Owen.

Geoffrey Laforge, the author of this thesis and first author of the published papers described in Chapters 2 and 3, was the primary contributor to all stages of the described investigations, including writing, experimental design, data collection, analyses, and interpretation. Adrian M. Owen and Bobby Stojanoski provided expert advice and supervision for all work described in this thesis and developed earlier iterations of the movie assessment paradigm cited throughout this thesis. Laura Gonzalez-Lara administered behavioural assessments to the cohort of patients with disorders of consciousness described in Chapter 2 and provided important feedback for this manuscript. Natalia Incio Serra recruited the French-speaking sample of healthy controls featured in Chapter 3 and organized participant scheduling and data collection. Stefanie Blain-Moraes helped conceive of the studies in Chapters 3 and 4 and assisted with the development of the experimental protocol outlined in Chapter 4.
Acknowledgements

This thesis, and the studies described within it, would not have been possible without the support of many extraordinary people. First and foremost, I would like to thank my supervisors Adrian Owen and Bobby Stojanoski. Without a doubt, Adrian and Bobby have been instrumental in shaping the scientist I am today. I have learned many, many things over the last six years, but I can credit Adrian for my deep appreciation for clear and effective science communication. Adrian regularly emphasized (and himself demonstrated) that excellent writing, engaging presentations, and thoughtful storytelling are invaluable aspects of the work we do. I took this to heart and it helped me to carve out my own voice, my own style, and my own place within the scientific community. However, none of this would be necessary—or even possible—without a strong scientific foundation. In this regard, I want to thank Bobby for fostering my scientific curiosity. Bobby encouraged me to explore unorthodox ideas as well as novel methodologies, and pushed me to think critically about all levels of my work, from minuscule details to implications for the “big picture”. I would also like to thank the wonderful members of the Owen Lab and, specifically, our ICU research team: Loretta, Karnig, and Sarah. This type of work is difficult to begin with and exponentially more so during a global pandemic. I would not have finished my thesis without their sustained efforts and commitment to our work together. Finally, I would like to acknowledge the role of my social supports, my friends and family, in finishing my Ph.D. In particular, I would like to thank my dear friend Josh. For years, Josh listened to a seemingly infinite stream of hairbrained ideas but was, nevertheless, there through all the ups and downs of graduate school. Josh is an excellent scientist, a genuine friend, and surely one of the best people I met in my time at Western. Above all, I owe all of my successes during the final years of my Ph.D. to my incredible and brilliant wife. While composing this thesis, she has been an endless source of inspiration, support, and encouragement. To her, I am forever grateful.
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Chapter 1

1 General Introduction

1.1 The (behavioural) problem of consciousness

Understanding the physiological basis of conscious awareness is one of the most profound problems facing modern neuroscience. Recent years have seen significant progress in identifying the neural correlates of consciousness and its supporting systems. However, fundamental questions concerning its properties, functions, as well as its necessary and sufficient conditions (e.g., after serious injury, in artificial systems) remain. While there are many competing definitions of conscious awareness (Del Pin et al., 2021; Zhao et al., 2019), in general, this refers to the existence of a rich internal experience in which a subject is aware of themselves and their environment (Frewen et al., 2020; Northoff & Lamme, 2020; Sattin et al., 2021). We know, intimately, what this awareness entails—what it feels like, for instance, to enjoy a hot cup of coffee or when we are fully immersed in an engaging movie—and we know what it is like when awareness is diminished, like during dreamless sleep (Bayne et al., 2016; Hobson & Pace-Schott, 2002; Windt et al., 2016; Zeman, 2001). However, given that consciousness is a subjective phenomenon, how can we objectively determine whether others have a comparable conscious experience? While this is an incredibly complex question, the answer in most contexts is relatively straightforward: we cannot know with absolute certainty that someone is conscious, but we can infer it on the basis of observable behaviour and verbal reports. In fact, our brains are primed to do precisely this.

Humans are uniquely social creatures; we engage in highly complex and dynamic social systems which require sophisticated coordination among multiple cortical networks to navigate effectively (Dunbar, 2009; Dunbar, 1998; Graziano & Kastner, 2011; Rosa Salva et al., 2015). One feature of this so-called “social brain” is the ability to detect other minds—to ascribe agency, awareness, and intentionality—in individuals who produce voluntary and goal-directed behaviour (Arico et al., 2011; Björnssssson & Shepherd, 2020). This occurs automatically when interacting with other people but also extends to certain species of non-human animals and to (seemingly) intelligent machines,
though to a much lesser extent (Arico et al., 2011; Nielsen et al., 2022; Urquiza-Haas & Kotrschal, 2015; van der Woerdt & Haselager, 2019). This ability, often referred to as mind-reading (or theory of mind), is extremely useful for navigating social situations; it helps reliably predict the future behaviour of others and supports interpersonal interactions (Adolphs, 2009; Brown & Brüne, 2012; Molapour et al., 2021; Thornton et al., 2019).

Outside of purely social contexts, observable behaviour and verbal reports remain the primary mechanisms through which we understand the mental states of others. Even in clinical settings, behavioural assessments of conscious awareness are the gold standard. For example, we can determine that a patient has woken up after major surgery once they begin to exhibit voluntary movements or respond to verbal commands (e.g., “raise your left hand”). While there are other informative physiological markers (Bodien et al., 2016; Martens et al., 2020; Teasdale & Jennett, 1974), behaviour is a ubiquitous and highly reliable indicator of conscious awareness (Kalmar & Giacino, 2005; Martens et al., 2020; Schnakers et al., 2009; Teasdale & Jennett, 1976). Nevertheless, there are several situations in which behaviour alone is insufficient to establish awareness or characterize conscious experience. Additionally, in many of these situations, accurate assessments of awareness are of critical importance.

It is generally accepted that conscious awareness is not synonymous with behaviour (but see Kotchoubey, 2018; Leslie, 2015); there are many instances in which the two become dissociated. Sleepwalkers, for example, appear to be awake but often do not exhibit any signs of awareness, nor do they report post hoc memories of the event, despite sometimes engaging in highly complex behaviour (Arnulf, 2018; Pressman, 2013). Absence (petit mal) seizures, too, can temporarily disrupt awareness without affecting arousal (wakefulness; Blumenfeld, 2012; 2005). Conversely, there are situations in which awareness is decoupled from behaviour. Dreaming is a clear example, where individuals experience a wide range of perceptual phenomena without corresponding overt behaviour (Hobson, 2009; Siclari et al., 2013; Tart, 2001). A more concerning example are cases of intraoperative awareness (IOA). IOA is a rare occurrence in which patients regain consciousness during an invasive medical procedure. Though temporary, IOA is highly
distressing and can cause lasting psychological harm to patients (Graham, Owen, Ipi, et al., 2018; Graham, Owen, Weijer, et al., 2018). However, IOA is extremely difficult to identify; patients who experience IOA cannot move and are thus unable to communicate their awareness through behaviour (Mashour et al., 2011). Techniques are being developed to detect IOA in real-time, but the mechanisms underlying this state are not well understood. As such, there are no valid and reliable tools to replace behavioural measures of awareness (Castellon-Larios et al., 2016; Graham, Owen, Ipi, et al., 2018; Huang et al., 2018; Loskota, 2005; Mashour et al., 2009, 2011).

Although phenomena like IOA have significant clinical implications, there are other circumstances in which awareness, or lack thereof, is used to guide the course of medical treatment (Hohwy & Reutens, 2009; Kahane & Savulescu, 2009). Indeed, apparent failure to recover conscious awareness after severe brain injury—whether in the initial acute stages or in the long term—can inform decisions about whether to withhold or withdraw life-sustaining therapy (Holland et al., 2014; Verheijde et al., 2009). Indeed, low likelihood of recovery or the prospect of severe, lasting impairments in cognitive functions, including those that support conscious awareness may lead substitute decision-makers to request a transition to end-of-life care (Lotto et al., 2012). While challenging, the decision to withdraw life-sustaining treatment in such cases is generally supported by physicians and members of the public, as chronic impairments in consciousness are commonly viewed as a worst-case outcome (Demertzi et al., 2011; Demertzi et al., 2014; Gipson et al., 2014; Graham, 2017; Payne et al., 1996). Severe brain injury, however, can differentially affect multiple areas of the brain (Cruse, Chennu, Chatelle, et al., 2012; Fernandez-Espejo et al., 2015). For example, patients may experience severe motor dysfunction but retain (or recover) some degree of awareness after their injury. In such instances, patients may be partially or fully conscious but unable to express their awareness during standardized behavioural assessments (Edlow et al., 2017; Laureys et al., 2005; Lutkenhoff et al., 2015; Martens et al., 2020; Osborne et al., 2015). In fact, this is precisely the situation for a small but significant number of patients diagnosed with a disorder of consciousness (DOC; Kondziella et al., 2016; Owen, 2008).
1.2 Disorders of consciousness

DOC are a class of rare neurological disorders broadly characterized by impairments in conscious awareness (Bernat, 2006; Laureys, 2007; Owen, 2008; Zeman, 2001). Common causes of DOC include traumatic brain injury (TBI), stroke, cardiac arrest, and cerebral hemorrhage (Cruse, Chennu, Chatelle, et al., 2012; Edlow et al., 2021). DOC encompass multiple diagnostic categories describing different degrees of dysfunction across two domains: wakefulness and awareness (Laureys, 2005; Laureys et al., 2009; Owen et al., 2006). These categories include coma, the vegetative state, and the minimally conscious state (Fins et al., 2007; Kalmar & Giacino, 2005; Kondziella et al., 2016; Tart, 2001). Coma is arguably the most severe form of DOC and occurs during the acute stages of severe brain injury. Patients in a coma remain entirely behaviourally non-responsive during assessments like the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) and do not exhibit any signs of wakefulness (i.e., eyes closed) or awareness. Coma will typically resolve within 2 – 4 weeks post-injury, but outcome trajectories from this state are highly variable (Laureys et al., 2001; Teasdale & Jennett, 1976; Wijdicks, 2012). Some patients will emerge from a coma and make a good recovery, while others may be diagnosed with brain death: an irreversible cessation of all brain function (Gosseries et al., 2011; Laureys et al., 2009). However, between these two outcomes are more complex diagnoses like the vegetative state and the minimally conscious state (Giacino et al., 2014; Owen, 2008).

After emerging from a coma, a small number of patients will transition into what is classically known as a vegetative state (now often referred to as Unresponsive Wakefulness Syndrome; UWS). The vegetative state is defined as a state of wakefulness without awareness (Laureys, 2007; Owen, 2008; von Wild et al., 2012). Patients in a vegetative state demonstrate eye-opening and closing behaviour indicative of sleep-wake cycles but do not appear to be aware of themselves or their environment (Cologan et al., 2013; Gibson et al., 2020). These patients may gaze at their surroundings and produce spontaneous motor movements or vocalizations but fail to respond during standardized behavioural measures of awareness like the Coma Recovery Scale-Revised (CRS-R Kalmar & Giacino, 2005). Patients may remain in a vegetative state for months or years.
without showing significant improvements (a “permanent” vegetative state; Giacino et al., 2018; Holland et al., 2014; von Wild et al., 2012). However, a substantial minority of patients may begin to produce inconsistent but reliable behavioural indicators of awareness over time and, thereby, meet the criteria for a diagnosis of minimally conscious (Burke, 2002; Fins et al., 2007; Kalmar & Giacino, 2005; Owen, 2008). The minimally conscious state encompasses a wide range of behavioural responsiveness, from the ability to localize pain or engage in visual pursuit (MCS minus) to command following (MCS plus; Bruno et al., 2011; Kondziella et al., 2017). Patients who continue to improve and become able to communicate or appropriately use functional objects are considered to have emerged from a minimally conscious state (EMCS; Giacino et al., 2018b; Lammi et al., 2005; Sun et al., 2018; Wang et al., 2020).

There are two other neurological conditions that mimic the behavioural dysfunctions seen in the vegetative state. The first, Locked-in Syndrome (LIS), occurs most frequently after brainstem stroke (Patterson & Grabois, 1986; Young, 2014). Like other types of severe brain injury, these patients will present in hospital with a decreased level of consciousness and remain non-responsive for days or weeks (Laureys et al., 2009). However, these patients will gradually regain conscious awareness but experience protracted quadriplegia, lower cranial nerve paralysis, and mutism due to the location of their injury (Gütling et al., 1996; Laureys, Pellás, Van Eeckhout, Ghorbel, Schnakers, Perrin, Berré, et al., 2005; Young, 2014). Therefore, patients with LIS are fully conscious but unable to move or speak, making early identification of their awareness exceptionally challenging. The second condition, Guillain-Barré Syndrome (GBS), is a rare—but usually transient—autoimmune disorder that damages the peripheral nervous system. Severe cases of GBS can cause ascending peripheral paralysis and lead to respiratory arrest, which can be fatal without the aid of mechanical ventilation (Progress et al., 2012; Shahrizaila et al., 2021). Notably, GBS does not appear to affect conscious awareness, vision, or hearing in most patients (Leonhard et al., 2019). As such, severe GBS, like LIS, can result in a state of hidden or “covert” awareness (i.e., without behaviour). While there are clear clinical distinctions between the clinical profiles of LIS, GBS, and DOC, their specific diagnostic criteria are often much less straightforward.
1.3 Behavioural diagnosis in disorders of consciousness

DOC are diagnosed using standardized behavioural measures of awareness like the GCS (Teasdale & Jennett, 1974) and the CRS-R (Kalmar & Giacino, 2005). The GCS is used to quantify the severity of head injury and diagnose acute coma. It is divided into three subscales: eye-opening, verbal responses to prompts from emergency care specialists, and motor responses to stimulation and commands (Bernat, 2006; Teasdale & Jennett, 1976; Teasdale & Jennett, 1974). GCS scores can range from 2T – 15, with scores below 9 indicating moderate to severe head injury with corresponding cognitive dysfunction and impaired awareness. The GCS is commonly administered on-site to rapidly assess patients with head injury and in hospital to track their recovery over time. Once patients recover from a coma, the CRS-R can be used to detect ongoing impairments in conscious awareness (Kalmar & Giacino, 2005; Teasdale & Jennett, 1974).

The CRS-R is a standardized neuropsychological assessment of awareness. It is divided into six subscales measuring visual, auditory, verbal, and motor function as well as a patient’s level of arousal and communication ability (Kalmar & Giacino, 2005). The subscales of the CRS-R are organized hierarchically where the first item on each scale tests reflex functions within each domain, and later items assess command following and cognitively-mediated behaviour (Kalmar & Giacino, 2005; Schnakers, Perrin, et al., 2009). Scores on the CRS-R range from 0 – 23, with lower scores indicating more severely impaired awareness (Kalmar & Giacino, 2005). The CRS-R provides behavioural diagnostic criteria for the vegetative state, the minimally conscious state, and emergence from a minimally conscious state based on a patient’s level of responsiveness during examination (Kalmar & Giacino, 2005; Schnakers, Vanhaudenhuyse, et al., 2009). This assessment should be administered regularly to track a patient’s level of function on a day-to-day basis and to detect signs of recovery over time. This is particularly important during the post-acute period when the likelihood of recovery is highest (Bagnato et al., 2017; Kalmar & Giacino, 2005; Noé et al., 2019; Pignat et al., 2016).

Currently, behavioural measures of awareness are the gold standard; neuropsychological assessments like the GCS and the CRS-R are the only clinically accepted tools to
diagnose DOC (Giacino et al., 2009; Kalmar & Giacino, 2005; Teasdale & Jennett, 1974). However, behavioural assessment is severely confounded by the sheer scope of serious brain injury. Perceptual, cognitive, and psychomotor dysfunctions are prevalent in cases of severe brain injury, which may outwardly present as a genuine lack of conscious awareness (Monti, Coleman, et al., 2010; Owen, 2008). Failure to respond during behavioural examinations may indicate any number of neuropsychological dysfunctions, including, but not limited to, those affecting awareness. Clinical diagnoses made on the basis of behaviour, therefore, may reflect these dysfunctions rather than provide an accurate description of a patient’s conscious state.

In fact, research over the last three decades has repeatedly demonstrated that the rate of misdiagnosis in DOC, and of the vegetative state specifically, is alarmingly high, with some estimates exceeding 40% (Andrews et al., 1996; Childs et al., 1993; Kondziella et al., 2016; Schnakers, Vanhaudenhuyse, et al., 2009). Additionally, similarities in the clinical presentations of LIS, GBS, and DOC further highlight the limitations of behavioural assessments. For example, patients with LIS often (but not always; Bauer et al., 1979; Carrai et al., 2009; Schnakers, Perrin, et al., 2009) regain control of vertical eye movement, but this may go undetected by clinical staff for extended periods (Bauer et al., 1979; Ragazzoni et al., 2000; Schnakers, Perrin, et al., 2009). Moreover, if not for the progressive nature of GBS, the resulting condition could be challenging to distinguish from DOC like coma or the vegetative state on the basis of behaviour alone (Formisano et al., 2013). Misdiagnosis in DOC has profound, far-reaching implications. Beyond (incorrectly) informing medical management and treatment, misdiagnosis has the alarming potential to erroneously inform decisions around end-of-life care (Graham et al., 2015; Schnakers et al., 2009; but see Wilkinson, Kahane, Horne, & Savulescu, 2009). It is therefore essential that we develop valid, reliable tools to assess conscious awareness without recourse to overt behaviour. One field of research that is leading the way in this regard is cognitive neuroscience (Fernández-Espejo & Owen, 2013; Owen, 2013).
1.4 Brain-based assessments of awareness

After severe brain injury, standardized behavioural assessments of awareness evaluate a patient’s ability to respond to environmental stimuli and verbal commands; measures like the CRS-R and the GCS approach this hierarchically to assess a patient’s specific level of function (Kalmar & Giacino, 2005; Teasdale & Jennett, 1974). For example, responses to simple stimuli (e.g., flexion withdrawal from applied pressure) reflect intact sensory function, whereas command following (e.g., functional object use) demonstrates the capacity to meaningfully interpret speech and execute an appropriate response. Importantly, these latter processes cannot occur without conscious awareness (but see Huang et al., 2018). In the context of behavioural assessment, however, command following is contingent on behavioural output, which can be challenging, if not impossible, for patients with injury-induced motor impairments (Cavaliere et al., 2014; Osborne et al., 2015). Moreover, impaired sensory processing or neuropsychological disorders like aphasia could limit a patient’s comprehension of verbal commands and prevent an appropriate motor response when otherwise possible (Fellinger et al., 2011; Gibson et al., 2014; Monti, 2012). Functional neuroimaging, on the other hand, can bypass the behavioural requirements of current assessment protocols and enable us to examine perception, cognition, and command following in patients with DOC at the level of the brain (Giacino et al., 2018a; Owen, 2008, 2013).

1.4.1 Covert command following and active tasks

Technologies like positron emission tomography (PET), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI) have been used extensively to characterize the different neurophysiological profiles of DOC (Laureys, 2005; Laureys et al., 2001; Laureys, Antoine, et al., 2002; Menon et al., 1998). Many studies have examined resting-state brain activity, evoked responses, and cortical processing in DOC but Owen and colleagues (2006) were among the first to use functional neuroimaging to probe conscious awareness directly. In this landmark study, Owen et al. used an fMRI motor imagery paradigm to investigate neural, rather than behavioural, command following. During scanning, they instructed healthy participants to imagine playing a
vigorous game of tennis or to imagine walking through the rooms of their home. They found that tennis imagery reliably increased blood-oxygen-level-dependent (BOLD) activity in the supplementary motor cortex—an area involved in coordinating complex motor movements. In contrast, spatial navigation increased BOLD activation in regions involved in spatial memory and attention like the parahippocampal gyrus, posterior parietal lobule, and lateral premotor cortex (Owen et al., 2006). They then asked one patient who was thought to be in a vegetative state to perform the same imagery task. Contrary to her diagnosis, she consistently and reliably produced patterns of neural activity that were statistically indistinguishable from healthy controls. Importantly, the findings from a follow-up study demonstrated that hearing the instructions alone was insufficient to produce the same patterns of BOLD activation observed in healthy controls and the patient; participants had to actively engage in the imagery task to produce a response (Owen et al., 2007). From these results, Owen et al. concluded that this patient, though behaviourally non-responsive, was, in fact, entirely aware (Owen et al., 2006, 2007).

In the years since, Owen and colleagues’ “covert” command following task has been used in larger cohorts of DOC patients and adapted for novel uses. For instance, Monti et al. (2010) found that 5 of 54 (9%) DOC patients scanned with fMRI could willfully modulate their neural activity during the motor imagery task. Moreover, they mapped the tennis and spatial navigation imagery to “yes” and “no” responses and established functional communication with one patient who remained entirely unresponsive during bedside behavioural assessment (Monti, Vanhaudenhuyse, et al., 2010). Additionally, Cruse and colleagues (2011) found similar results when testing a comparable bedside version of this paradigm. Indeed, Cruse et al. detected imagined movements (e.g., “Imagine squeezing your right hand/wiggling all of your toes”) in 3 of 16 (19%) DOC patients using EEG—a low cost, portable, and widely available neuroimaging device (Cruse, Chennu, Fernández-Espejo, et al., 2012). More recently, Edlow et al. (2017) reported that 4 of 8 (50%) patients with acute DOC could reliably perform hand squeeze imagery in fMRI, including two patients in an acute coma (i.e., eyes closed, behaviorally non-responsive).
Motor imagery tasks are a highly effective method to identify residual awareness in some DOC patients. However, the proportion of responders is considerably lower than the estimated rates of misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Schnakers, Vanhaudenhuyse, et al., 2009). This may be due, in part, to the high cognitive demands of mental imagery; having to repeatedly imagine complex actions may be challenging for patients with DOC (Cruse et al., 2011a; Naci et al., 2014). One way to address this issue is to build from these earlier techniques (i.e., use cognition as a proxy of overt behaviour) and develop novel neuroimaging assessments that incorporate different aspects of neural and cognitive function. For example, a case study by Monti et al. (2013) describes one non-responsive individual who could direct their visual attention on command—as indexed by changes in BOLD activity in the visual cortex—to correctly focus on one of two competing visual stimuli. Similarly, Naci and Owen (2013) found task-related modulations of hemodynamic activity in three DOC patients (two minimally conscious, one vegetative) corresponding to volitional shifts in auditory attention. Like motor imagery, identifying neural correlates of top-down attention can provide strong evidence of covert awareness; selective attention cannot be deployed or controlled in the absence of conscious awareness (Gibson et al., 2016; Monti et al., 2013; Naci et al., 2013; Naci & Owen, 2013). Yet, also like motor imagery, attentional modulation and similar “active” tasks are not ideal for patients with severe brain injury. During active paradigms, patients are tasked with modulating their neural activity in a highly circumscribed manner, at a specific time, for a pre-determined duration, and often multiple times across trials (Møller et al., 2020). Each of these factors compounds the cognitive demands of the task and its complexity, which can increase to patient fatigue and lead to inconsistent responding (Berlingerí et al., 2019; Cruse et al., 2011a; Møller et al., 2020). The results from a recent meta-analysis on neuroimaging in DOC suggest this as well, with studies that use active tasks reporting evidence of preserved conscious awareness in just 24% of patients (Kondziella et al., 2016). In sum, while active tasks can provide clear evidence of covert awareness, they may not be suitable for all patients with DOC (Kondziella et al., 2016; Møller et al., 2020).
1.4.2 Passive paradigms and diagnostic classification

Studies that use “passive” neuroimaging tasks report evidence of preserved conscious awareness in 38% of DOC patients—more closely approximating the rate estimated rate of misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Kondziella et al., 2016; Schnakers, Vanhaudenhuyse, et al., 2009). Passive neuroimaging paradigms do not require patients to perform a task or willfully modulate their neural activity. Instead, passive tasks aggregate spontaneous (i.e., rest) or evoked activity to assess perceptual processing, cognitive function, and covert awareness. Resting-state neuroimaging, in particular, has been used extensively to describe the neurophysiological deficits of DOC. Indeed, resting-state EEG, PET, and fMRI activity played an essential role in linking neural dysfunction to the behavioural impairments observed in disorders like coma and the vegetative state (Laureys et al., 2001, 2004; Laureys, Antoine, et al., 2002; Owen et al., 2002; Owen & Coleman, 2007).

More recently, advances in neuroimaging technologies and computational analysis techniques have enabled researchers to extract hidden features from resting-state activity to better inform diagnosis and prognosis in DOC. A study by Chennu et al. (2017), for instance, demonstrated that EEG spectral connectivity at rest corroborates behavioural assessments of awareness and correlates strongly with glucose metabolism in patients with DOC. Moreover, EEG network connectivity predicted outcomes at one year and, crucially, detected neural markers of preserved awareness in unresponsive patients who would later be re-diagnosed as minimally conscious (Chennu et al., 2017). In critical care settings, too, resting-state neuroimaging has been associated with quality of outcome. For example, O’Donnell et al. (2021) found that mean EEG alpha power improved prognostic accuracy at three months in patients with acute DOC, relative to clinical measures alone.

Passive neuroimaging paradigms can also include evoked and event-related designs. These involve presenting patients with auditory, visual, or somatosensory stimuli to assess their automatic neural responses (Beukema et al., 2016; Gibson et al., 2016; Laureys, Faymonville, et al., 2002; Owen et al., 2005). Evoked and event-related paradigms are often organized hierarchically to examine different levels of neural
function—from basic sensory processes to those that are cognitively mediated. A foundational study by Kotchoubey et al. (2005) used this hierarchical approach to investigate cortical processing in a cohort of vegetative and minimally conscious patients. Briefly, they recorded patients’ EEG activity during a passive auditory processing task and examined the corresponding event-related potentials (ERPs) to increasingly complex stimuli. They found that most patients showed the classic N1 – P2 complex indicative of primary auditory processing during trials with simple tones. However, fewer than half produced a mismatch negativity or a P3 attentional orienting response which would signal the detection of deviant “oddball” stimuli embedded in repeating auditory patterns. Finally, only 18% of patients showed an N400 semantic error detection response during trials with incongruent word pairs (e.g., “chair – mouse” vs. “chair – table”) or anomalous sentences (e.g., “I drink tea with shoes”).

More recent studies have reported similar results using comparable passive EEG tasks. Beukema et al. (2016), for example, found that 44% of chronic DOC patients produced ERPs indicative of speech-noise differentiation, whereas just 6% showed an N400 to incongruent word pairs. Additionally, Sokoliuk and colleagues (2021) demonstrated that EEG inter-trial phase coherence during a passive speech tracking task—a measure of conscious semantic processing—improved the accuracy of prognosis in acute DOC. Specifically, patients who produced the appropriate (i.e., similar to healthy controls) neural response to auditory phrases and sentences had higher scores on the Glasgow Outcome Scale Extended (GOSE; Teasdale et al., 1998) at 3 and 6 months than those who did not. Taken together, these findings suggest that a significant majority of patients with chronic and acute DOC experience persistent impairments in cognitive functions like attention and semantic processing (Beukema et al., 2016; B. Kotchoubey et al., 2005; Sokoliuk et al., 2021). While this does not apply to all patients, novel neuroimaging assessments should take these considerations into account.

Passive neuroimaging paradigms can be extremely useful to identify specific neural and cognitive dysfunctions in DOC patients, both at the group level (e.g., common impairments in the vegetative state) and among individual patients (Beukema et al., 2016; Kotchoubey et al., 2005; O’Donnell et al., 2021). At the same time, they can also uncover
neural evidence of preserved function, which can further inform clinical diagnosis and
prognostication of outcome (Chennu et al., 2017; Kondziella et al., 2016; O’Donnell et
al., 2021; Pauli et al., 2020). Nevertheless, resting state and evoked or event-related
designs have notable limitations. First, the scope of resting-state neuroimaging is highly
constrained; little can be gleaned about the conscious experiences of DOC patients from
neural activity at rest. Likewise, evoked and event-related designs share some of the same
practical and methodological limitations as active ones. For example, evoked and event-
related tasks often use multiple stimulus types to compare levels of function, each
requiring several trials to detect a neural response (Beukema et al., 2016; Cruse et al.,
2011b; B. Kotchoubey et al., 2005). While this may not affect assessments of lower-level
processes (e.g., primary sensory function), decreased attention, vigilance, or arousal over
time could increase the likelihood of null findings during more cognitively demanding
trials, irrespective of a patient’s level of awareness (Berlingeri et al., 2019; Kondziella et
al., 2016). More broadly, evoked or event-related activity is a proxy measure of
perceptual and cognitive ability; how well these generalize to other contexts is not well
understood.

Limitations notwithstanding, decades of neuroimaging research in chronic and acute
DOC have produced a remarkable number of brain-based assessments that examine a
wide range of physiological, neural, and cognitive domains. While the specific techniques
vary considerably, most assessments share one of two goals: 1) to elucidate the
etiological and physiological factors that contribute to the development and preservation
of DOC or 2) to improve diagnostic and prognostic accuracy using neuroimaging. To an
extent, both lines of research are primarily concerned with clinical classification in DOC;
for example, whether identifying the neurophysiological differences between the
vegetative and minimally conscious state (Goal 1) or detecting residual awareness in
behaviourally non-responsive patients and upgrading their clinical status (Goal 2). These
approaches have contributed significantly to our understanding of DOC and have led to
marked improvements in patient welfare. However, to date, relatively few studies have
aimed to characterize the experience of these patients; to examine what it is like to be in
this altered state of awareness. Neural assessments of DOC typically focus on discrete
responses to contrived or unnatural stimuli rather than examine wholistic neural processes. This approach limits our ability to extrapolate a patient’s true level of cognitive function outside of these narrow contexts (Naci et al., 2014, 2015). One way to address this is to use more naturalistic assessments of cognitive function and conscious experience in patients with DOC.

1.4.3 Naturalistic neuroimaging paradigms

Naturalistic experimental paradigms mimic real-world situations or use commonplace stimuli like music, movies, or stories that readily capture and sustain attention. Unlike active tasks or event-based designs, naturalistic paradigms use dynamic, multidimensional, and continuous stimuli. Movies are an excellent example; they contain complex auditory and visual information that rapidly changes within and between scenes. One feature, in particular, that makes movies unique is their plot. Movies unfold dynamically around a central narrative that, itself, contains several elements that transcend its physical and semantic properties (i.e., audio-visual information, dialogue). Properties like a movie’s suspense, for instance, are inferred by the viewer from narrative cues and executive processes like working memory and theory of mind—understanding what characters do and do not know about themselves, their circumstances, or other characters. Importantly, to experience these “higher-order” properties, viewers must attend to the movie and comprehend its plot—processes that require conscious awareness (Naci et al., 2014, 2015).

Despite their dynamic and complex nature, movies tend to elicit a consistent neural response across individuals (Chen et al., 2017; Hasson et al., 2010; Naci et al., 2014; Nguyen et al., 2017). Indeed, Hasson et al. (2004) found that neural activity “synchronized” across participants during naturalistic viewing conditions (i.e., movie-watching). In this study, they presented a 30-minute clip from the feature film “The Good, The Bad, and The Ugly” to a group of healthy participants during an fMRI scan. Using an inter-subject correlations (ISCs) analysis—a procedure that uses the hemodynamic time course of a voxel in one subject to predict activity in the corresponding voxel in another—they determined that, on average, nearly 30% of the
cortical surface was significantly correlated across the group during the movie. This “synchronization” included most of the primary visual and auditory cortices, as well as somatosensory and multimodal association areas, and regions of the cingulate gyrus. Crucially, they did not find any significant correlations across participants during a resting-state control condition, demonstrating that inter-subject synchronization is not a natural state of the brain but rather one driven by the movie (Hasson et al., 2004).

Hasson and colleagues also examined the time course of ISCs within activated regions to track neural synchronization over the duration of the movie. Using the temporal ISCs, they reconstructed the events of the film that significantly increased ISCs in specific brain regions. For example, they found peak ISCs in the fusiform gyrus during close-ups on characters’ faces, whereas ISCs in the post-central sulcus were highest for scenes with hands performing various motor tasks (Hasson et al., 2004). Bartels and Zeki (2004a, 2005) also reported comparable results using different movie stimuli, suggesting that this phenomenon is not constrained to a single stimulus. Overall, Hasson et al. and Bartels and Zeki not only demonstrated that participants’ neural activity synchronized across the brain during movie-watching tasks but that it does so in a highly coordinated manner to code the individual features of each scene. From these studies, however, it remained unclear whether higher-order properties of movies like suspense were similarly processed across individuals.

Naci et al. (2014) aimed to address this question by investigating which cortical networks coded different aspects of the movie-watching experience, including suspense. Like Hasson et al. (2004), Naci and colleagues calculated ISCs across a group of 12 individuals who watched an abridged version of Alfred Hitchcock’s “Bang! You’re Dead” during an fMRI scan. The film (described in detail in Chapter 2) depicts a boy who finds his uncle’s revolver and plays with it as it were a toy (e.g., pointing it at other characters, spinning the chamber, pulling the trigger). The other characters in the film do not know the boy has replaced his toy gun with a real one, and the viewers do not know, moment to moment, whether the chamber of the gun is loaded. In this way, Hitchcock masterfully builds suspense using narrative elements of the movie—those that require
executive processes like theory of mind, working memory, and prediction of future events—rather than its physical properties (e.g., audio volume).

Naci and colleagues (2014) hypothesized that, in addition to sensory areas, frontoparietal “executive” regions of the brain—those associated with cognitive processes like attention, working memory, and theory of mind—would synchronize across viewers. Using the ISCs analysis, they found significant brain-wide neural synchronization across participants during the movie, spanning primary and secondary sensory areas, association cortices, and areas of the frontal and parietal lobes. However, significant ISCs in frontoparietal executive regions are not, in themselves, indicative of shared processing of the movie’s suspense; language processing, eye movements, and multimodal sensory integration involve these regions as well. To rule out the possibility that these processes contributed significantly to frontoparietal synchronization, Naci et al. also presented a scrambled version of “Bang! You’re Dead” to the same participants. This version consisted of 1s clips of the movie that Naci and colleagues pseudo-randomly rearranged to eliminate any semblance of the plot. When they compared the map of ISCs between conditions, they found significantly higher synchronization frontoparietal areas of the cortex during the intact movie. Finally, they did not find any significant inter-subject neural synchronization during a resting-state control condition, lending additional support to the findings of Hasson and colleagues (2004).

Using a group-level independent components analysis (ICA), Naci et al. (2014) explored which cortical networks—rather than individual regions—reliably synchronized across viewers. They grouped the independent components into five spatially distinct functional networks: auditory, frontoparietal, visual, motor, and precuneus. Single-subject ICA verified that the group-level ISCs observed in these networks were reliable across subjects, and a leave-one-out procedure validated that the time course of the components remained significantly correlated across all participants. While the auditory network explained the most variance in ISCs at the single-subject level, the components of the frontoparietal network ranked second-highest during the intact movie condition. These findings supported the hypothesis that executive processes drove a significant proportion of the ISCs across the group (Naci et al., 2014).
Naci and colleagues took this one step further by correlating the time course of the movie’s executive load to the ISCs in the frontoparietal network. To accomplish this, they asked an independent group of volunteers to watch “Bang! You’re Dead” while performing the sustained attention to response task (SART). The SART is a dual-task variant of the go-no-go paradigm where participants provide a speeded-key press response to hearing “go” numbers (1 – 7 and 9) but withhold a response to a “no-go” number (8). The SART assumes that executive functions like attention, working memory, and motor inhibition are finite resources. Increased executive demands during the movie (i.e., during peak periods of suspense) would, therefore, deplete these resources and decrease accuracy during the task (Manly et al., 1999). When they analyzed the response characteristics from participants over time, they found that shorter reaction times reliably preceded a failure to withhold a response to the “no-go” number. This indicated a transition to automatic responding (i.e., reduced cognitive control) associated with increased executive load during the movie. Naci et al. used the results from the SART as a regressor in their fMRI data and found that these changes in reaction times significantly predicted the time course of activity in the frontoparietal executive network.

After finding that objective measures of executive load predicted frontoparietal activation during the movie, Naci and colleagues (2014) investigated the influence of suspense on frontoparietal function directly. For this analysis, they asked an independent group of volunteers to rate how much suspense they felt during 2s segments of “Bang! You’re Dead” from least suspenseful to most suspenseful. Like the SART, continuous suspense ratings provide an index of the movie’s executive demands over time. Suspense develops when viewers process the higher-order elements of an engaging film and use these to form and update models of each character’s mental state, understand the potential consequences of their actions, and predict the outcome trajectories of the story. Feelings of suspense, then, suggest significant deployment of executive resources like attention, working memory, and theory of mind necessary to follow the plot of a movie. Naci et al. found that suspense ratings of “Bang! You’re Dead” were tightly correlated between individuals suggesting a similar conscious experience of the movie and, when used as a
regrressor in the fMRI analyses, predicted the time course of activity in frontoparietal executive regions.

Overall, these findings highlight the significant contributions of the frontoparietal executive network during movie-watching (Naci et al., 2014). Additionally, significant ISCs in frontoparietal BOLD activity during the intact version of the “Bang! You’re Dead” (or rest) suggested that participants were comparably engaged in the higher-order features of the movie, rather than simply responding to its sensory properties. Naci and colleagues then tested whether frontoparietal activity elicited during the movie could be used to assess awareness in patients with DOC. For the last experiment of this study, Naci et al. presented “Bang! You’re Dead” to two behaviourally non-responsive patients while recording their BOLD activity using fMRI.

Patient 1 was rendered behaviourally non-responsive by progressive encephalopathy. Repeated bedside assessments resulted in behavioural diagnoses that fluctuated between a vegetative state and a minimally conscious state; she exhibited intermittent evidence of visual tracking, but this was unreliable across assessments. However, given the behavioural constraints of measures like the CRS-R, it was entirely possible that she retained some degree of awareness but simply could not express it. If this were the case, perhaps she would show brain-based evidence of residual conscious processing during the movie task. Naci et al. (2014) presented “Bang! You’re Dead” to Patient 1 during an fMRI scan and used the same single-subject components analysis to compare her neural activity to the group of healthy controls. They found significant neural synchronization between Patient 1 and the control group in the auditory network but not in visual or frontoparietal regions. While this suggested that she retained residual auditory function, it was unclear whether this information reached her awareness; cortical reactivity to auditory stimuli is typically preserved in patients with DOC, but this activity is generally confined to primary sensory regions (Boly et al., 2004; Henriques et al., 2016; Laureys et al., 2000).

Patient 2 suffered a hypoxic brain injury leading to coma. The coma resolved after three weeks but he remained behaviourally non-responsive and was diagnosed as being in a
vegetative state. However, more recent behavioural assessments suggested that his diagnosis, like Patient 1, fluctuated between a vegetative state and a minimally conscious state. Naci et al. (2014) repeated the single-subject components analysis on the fMRI data from Patient 2 during the movie, which revealed significant ISCs in auditory, visual, and frontoparietal cortical networks. While this alone suggested that he could process the higher-order narrative elements of “Bang! You’re Dead”, the time course of activity in his frontoparietal network was also significantly correlated to the SART and suspense ratings data. Altogether, these results strongly suggest that Patient 2 could process the movie in a way that closely resembled healthy controls and was, thus, consciously aware.

With these results, Naci et al. (2014) demonstrated that the consistency of neural activity across participants during naturalistic stimulation index, to a certain extent, the similarity of their conscious experience of the movie. Significant ISCs in the frontoparietal network during the intact version of “Bang! You’re Dead”, combined with their temporal correspondence to quantitative (SART) and qualitative (suspense ratings) measures of its executive demands over time, suggested that participants were similarly engaged in the movie’s narrative. What’s more, this technique revealed neural markers of auditory processing in two patients with chronic DOC, as well as visual and narrative processing in one who remained minimally responsive at the time of assessment—without recourse to overt behaviour, active responding, or multiple trials. In this way, tasks that use naturalistic stimuli like the one presented by Naci et al. (2014) may be an especially powerful tool to assess sensory function, cognition, and covert awareness in patients with DOC. However, the findings from Patient 1 raise important questions about the task’s design.

Both patients met the criteria of minimally conscious on the day of testing. Yet, Naci et al. (2014) only observed visual and frontoparietal synchronization in Patient 2. Evidence of auditory synchronization in Patient 1 suggested that she could process the auditory features of “Bang! You’re Dead” in a way that resembled healthy controls, but not its visual or narrative elements. This could be due to any number of factors, including a genuine lack of the cognitive functions required to follow the movie’s plot. However, it remains possible that Patient 1 suffered residual visual impairments, precluding her from
experiencing this dimension of the movie (Naci et al., 2014). As “Bang! You’re Dead” relies heavily on visual information to progress the story, an inability to effectively process this information could have limited her engagement with the film and her subsequent frontoparietal response (Naci et al., 2015).

A follow-up study by Naci et al. (2015) aimed to determine whether naturalistic auditory stimuli alone could yield a similarly robust frontoparietal executive response. Patients with DOC typically retain auditory function (Boly et al., 2004; Henriches et al., 2016; Laureys et al., 2000). Therefore, a neural assessments paradigm that relies on auditory processing may be better suited to most patients. Additionally, reducing the number of perceptual domains involved during the task (i.e., audio-visual to audio-only) may minimize its cognitive demands. Using fMRI, Naci et al. piloted two types of auditory stimuli in a group of healthy volunteers: suspenseful instrumental pieces and a short audio clip from the movie “Taken”. Naci et al. hypothesized that, despite the absence of speech or dialogue, the suspenseful nature of the instrumental pieces might be sufficient to drive a frontoparietal executive response like the one observed for “Bang! You’re Dead”. The audio clip from “Taken” (described in detail in Chapter 2) depicts a phone conversation between a father and daughter while she is trying to evade kidnappers. She is eventually found and taken away, which can be heard by her father on the other end of the call. Unlike “Bang! You’re Dead”, suspense during “Taken” builds rapidly due to the nature of the subject matter and is aided by sounds effects and atmospheric music. Like their previous study, Naci et al. also presented a scrambled version of the “Taken” audio. This version had been spectrally rotated to preserve the physical characteristic of the stimulus but remove the speech and dialogue necessary to convey the story.

During the suspenseful instrumental pieces, Naci et al. (2015) found significant ISCs across bilateral auditory cortices, but this did not extend to frontal or parietal regions. However, the intact version of “Taken” produced significant brain-wide ISCs across the group, whereas ISCs remained significant in primary and association cortices during the scrambled version. A subtraction procedure between the ISCs maps of the intact and scrambled audio conditions revealed significantly higher inter-subject synchronization in motor, temporal, frontal and prefrontal, and parietal areas during the intact version of
“Taken”. Like “Bang! You’re Dead”, group-level ICA uncovered many spatially distinct components, including those that constitute the frontoparietal executive network. Single-subject frontoparietal time courses were significantly correlated to the group-level network and, conversely, the group-level time course predicted frontoparietal activity in all but one subject after a leave-one-out analysis.

1.5 Summary and Aims

Neural assessments of awareness in patients with DOC have evolved considerably since Owen et al. (2006) first established contact with one behaviourally non-responsive patient using fMRI. A multitude of covert command following tasks and active paradigms have been developed to assess awareness in DOC directly, and several resting state and passive techniques have been proposed to examine neural function after severe brain injury. Passive naturalistic paradigms share the strengths of both classes of assessments. Over two studies, Naci and colleagues (2014, 2015) demonstrated the utility of using naturalistic movie stimuli to assess frontoparietal executive function—a proxy measure of awareness—in healthy controls and in patients with chronic DOC. This approach eschews many of the practical and methodological limitations of previous assessment techniques; it does not rely on overt behaviour or covert responding. Additionally, this assessment is rapid, only requiring a single trial, and the stimuli are naturally engaging but sufficiently complex to investigate higher-order cognitive functions.

However, the use of fMRI in DOC populations presents a number of significant challenges. First, fMRI scanners are not widely available in hospitals or outpatient care centers, limiting access for a significant number of patients. The costs associated with using fMRI, likewise, prohibit routine assessments. Additionally, patients with serious brain injury often move involuntarily, which can severely contaminate fMRI data, and many are not medically suitable for fMRI, especially in the acute stages of injury. EEG, on the other hand, is a low-cost and portable neuroimaging device that can be rapidly applied at a patient’s bedside. EEG has fewer exclusion criteria than fMRI and is routinely used in critical care settings and outpatient facilities. Although EEG does not have the same spatial resolution as fMRI (but see Asadzadeh et al., 2020; Michel &
Brunet, 2019), its temporal precision can track moment-to-moment changes in neural activity at millisecond time scales. For these reasons, EEG is an attractive alternative to fMRI for the routine assessment of awareness in patients with chronic and acute DOC. However, few studies to date have evaluated the feasibility of using naturalistic EEG paradigms to index executive processes in DOC patients (Iotzov et al., 2017).

Building upon the work of Naci et al. (2014, 2015, 2018), the primary goal of this thesis was to develop and validate an EEG assessment of naturalistic processing in patients with chronic and acute DOC. The following chapters will describe a novel analysis technique designed to capture ISCs in EEG activity, present normative and patient data to support the efficacy of this approach, and lay the groundwork for future investigations in a broader range of clinical populations. All experimental procedures and statistical analyses were piloted in healthy control participants and validated in patients with chronic and acute DOC. This thesis is divided into three experimental sections, each with its own specific motivations and aims, briefly described below.

The study presented in Chapter 2 describes one approach to quantify inter-subject neural synchronization of EEG activity during “Bang! You’re Dead” and “Taken”. This study predominantly focused on the computational processes of calculating ISCs from group-level EEG activity. We present the findings from multiple validation analyses performed to ensure that ISCs were reliable across participants and indexed the same executive functions reported by Naci et al. (2014, 2015). These validation steps included a leave-one-out procedure for calculating group-level ISCs, calculating time-resolved ISCs and correlating these time courses to subjective suspense ratings, and performing a source localization analysis to uncover the cortical sources of the ISCs during the “Taken” audio. Finally, we present the results from a cohort of DOC patients who participated in this EEG assessment and discuss the diagnostic implications of our findings.

For the second study of this thesis, detailed in Chapter 3, we compared ISCs from two groups of healthy controls—one English-speaking group and one French-speaking group—who listened to the “Taken” audio in their mother tongue. The motivation for this study was to determine whether the EEG “Taken” paradigm performed comparably well
when translated to another language, potentially increasing the range of its application in DOC patients across Canadian care centers. Here, we describe the results from our ISCs analysis, as well as a time-resolved version for both groups and examine whether these correspond to subjective suspense ratings. We also address issues around timing discrepancies for both sets of stimuli and propose methodological approaches to appropriately implement this assessment in cohorts of French-speaking DOC patients.

The last study of this thesis is presented in Chapter 4. Here, we examined the feasibility of applying the EEG “Taken” assessment paradigm to identify covert cognitive function in patients with severe acute brain injury. We presented the audio to a cohort of acutely comatose patients\(^1\) while they received continuous pharmacological sedation and again after was withdrawn. We aimed to determine whether the change across three distinct EEG measures—ISCs, functional connectivity, and cortical source reconstruction—predicted later outcomes. This study details the computational and statistical procedures underlying each analysis technique and compares results on each measure to individual patient outcomes. Finally, we evaluate the prognostic value of the original ISCs analysis in acutely comatose patients and identify patterns of EEG connectivity and cortical sources that differentiate patients with good and poor clinical outcomes.

\(^1\) Please note that the COVID-19 pandemic severely limited the number of patients that could be enrolled in this study.
References


Chapter 2

2 Individualized assessment of residual cognition in patients with disorders of consciousness

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2.1 Introduction

A small but significant number of patients who survive severe brain injury will progress to a state of altered awareness known as a disorder of consciousness (DOC). Patients with DOC exhibit regular periods of wakefulness but produce minimal or inconsistent behavioural evidence of conscious awareness. This presents a considerable challenge for clinicians when trying to accurately diagnose a patient’s conscious state, as available clinical measures like the Coma Recovery Scale-Revised (CRS-R; Kalmar and Giacino, 2005) rely on observable behavioural responses to verbal commands. In some cases, a lack of purposeful behaviour may reflect a true absence of awareness—a condition known as the vegetative state. However, expert reassessments of DOC patients consistently show that approximately 40% of these patients are, at least, minimally conscious (Andrews et al., 1996; Burke, 2002; Childs et al., 1993; Schnakers et al., 2009). While repeated behavioural assessments may reduce the rate of misdiagnosis of patients with DOC, acquired cognitive or physiological impairments may still preclude behavioural expressions of awareness in many patients. Because of these limitations, novel brain-based assessments have been proposed as an alternative to behavioural testing.

To date, several studies have demonstrated that neuroimaging techniques, such as functional MRI (fMRI) and electroencephalography (EEG), can be used to capture the
neural correlates of awareness in patients with DOC. For example, Owen et al. (2006) developed an fMRI motor imagery task to assess “covert” (rather than behavioural) command-following. In that study, the unique patterns of brain activity elicited by different types of imagined motor imagery (e.g., playing tennis, spatial navigation) were used to determine whether patients could correctly modulate their neural activity in response to specific task instructions. One patient, who appeared to be entirely vegetative, could reliably produce the appropriate neural response to each imagery command, providing strong evidence of her awareness. Similar imagery paradigms have since been used to examine larger cohorts of patients using either fMRI (Monti et al., 2010) and, more recently, EEG (Cruse et al., 2011). Yet, the active nature of imagined command-following tasks, much like their behavioural counterparts, requires the coordination of several cognitive faculties, as well as sustained periods of vigilance and effort, that may prove difficult for some patients and impossible for others. Indeed, a recent review found that just 14% of behaviourally non-responsive patients could modulate their brain activity in response to verbal commands (Kondziella et al., 2016), which is far lower than the estimated 40% who are known to be misdiagnosed (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009).

As a result, recent studies have moved towards using naturalistic tasks that more closely mimic real-world activities. Movie-watching has emerged as a particularly useful paradigm; previous research has shown that watching suspenseful movies such as Alfred Hitchcock’s “Bang! You’re Dead” produces significant brain-wide correlations between healthy controls (Hasson et al., 2004, 2010; Naci et al., 2015). This “synchronization” spans primary sensory regions as well as areas of the frontal and parietal cortices that are involved in executive functions like theory of mind and attentional control (Naci et al., 2014, 2015), both of which are necessary to follow the plot of a movie. Naci and colleagues (2014) capitalized on this phenomenon to create an fMRI movie-watching paradigm for assessing executive processing in patients with DOC. They showed that the degree of frontoparietal synchronization between participants during “Bang! You’re Dead” significantly correlated with measures of suspense and executive load. Furthermore, the same highly-correlated brain responses occurred in one patient who met
the behavioural criteria for a vegetative state diagnosis. On this basis, the authors were able to conclude that the patient was, in fact, aware, despite his behavioural and clinical profile.

However, for naturalistic approaches to be clinically viable, they must be moved to the bedside. In this regard, EEG is the ideal neuroimaging tool for assessing residual cognitive function in patients with DOC; EEG is portable, widely available in clinical settings, and it minimizes the cost of routine neural assessments, as well as the physical toll incurred by patients during fMRI testing (Cruse et al., 2011). To this end, we hypothesized that EEG could be used to assess the level of inter-subject synchronization (or inter-subject correlations; ISCs), and therefore identify markers of executive processing in patients with DOC. As such, the aim of this study was to develop a bedside neuroimaging paradigm to assess ISCs during movie tasks in patients with DOC.

2.2 Materials and methods

2.2.1 Patients and controls

We recruited a convenience sample of 13 patients with severe traumatic and non-traumatic brain injuries who met the CRS-R (Kalmar & Giacino, 2005) diagnostic criteria for DOC (see Table 1 for clinical information). At the time of testing, ten patients met the clinical criteria for the vegetative state, two were in a minimally conscious state, and one was diagnosed with Locked-in Syndrome. Informed assent was obtained from substitute decision-makers and medical care teams for all patients. All healthy participants were recruited from The Brain and Mind Institute at the University of Western Ontario, Canada (Appendix A). Twenty-eight healthy volunteers took part in the EEG portion of this study, and an additional 40 performed a follow-up behavioural task. Informed written consent was acquired prior to testing.

Ethics approval for this study was granted by the Health Sciences Research Ethics Board and the Non-Medical Research Ethics Board of The University of Western Ontario.
2.2.2 Procedures

All patients were assessed with the CRS-R on the day of testing. The CRS-R consists of six subscales evaluating sensory and motor function, communication ability, and level of arousal, to distinguish patients who are minimally conscious—those who exhibit intermittent behavioural evidence of awareness—from patients who are in a vegetative state (Kalmar & Giacino, 2005).

We used two suspenseful movie clips to measure ISCs between healthy controls and individual patients with DOC. The first clip was an 8-minute audiovisual segment from the Alfred Hitchcock TV movie “Bang! You’re Dead”. Briefly, this scene portrays a 5-year-old boy who finds his uncle’s revolver. Being unaware of its danger, the boy partially loads the gun and plays with it as if it were a normal toy. The viewer (and the boy himself) is rarely privy to whether the gun has a bullet in its chamber, and suspense continues to build the longer the boy plays with the gun (e.g., spinning the chamber, pointing it at others, pulling the trigger). To account for potential visual impairments among DOC patients, we also used a second clip comprised of a 5-minute audio excerpt from the movie “Taken. In this clip, the listener hears a phone conversation between a

Table 1. Clinical and Demographic Information for Patients with Disorders of Consciousness

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Assessment (years)</th>
<th>Sex</th>
<th>Clinical Diagnosis</th>
<th>Etiology</th>
<th>Interval postictus (days)</th>
<th>CRS-R at Assessment (/23)</th>
<th>Movie Condition (s)</th>
<th>Significant ISC</th>
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<tr>
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<td>3647</td>
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<td>TKN*</td>
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<td>1148</td>
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<td>-</td>
</tr>
<tr>
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<td>Both</td>
<td>TKN*</td>
</tr>
<tr>
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<td>8427</td>
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<td>BYD*</td>
</tr>
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<td>Anoxia</td>
<td>314</td>
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<td>-</td>
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</tbody>
</table>

Note. VS, Vegetative State; MCS, Minimally Conscious State; LIS, Locked-in Syndrome; TBI, traumatic brain injury; CRS-R, Coma Recovery Scale-Revised; BYD, “Bang! You’re Dead”; TKN, “Taken”. * denotes significant ISC with controls, p < 0.05; ** denotes significant ISC with controls for both movie tasks, p < 0.05.
father character and his daughter, who is away on vacation. The conversation quickly changes tone as she becomes aware of kidnappers in her accommodation. The kidnappers eventually discover where she is hiding and take her away—all of which can be heard over the father’s end of the call. Unlike “Bang! You’re Dead”, the suspense in this clip builds much less subtly, relying more on atmosphere and intensity than unpredictability. This brute-force approach to building suspense was taken into account when initially testing this clip (Naci et al., 2015), since driving synchronization with audio alone is more difficult than with visual or multimodal stimuli (Dmochowski et al., 2017; Naci et al., 2015). Both movies have been rated as highly suspenseful and produce robust ISCs between healthy volunteers in fMRI (Naci et al., 2014, 2015). We also used two “scrambled” control stimuli, one for each movie, to separate the neural responses elicited by the sensory properties of watching or listening to the movies from those involved in following the plot. The scrambled version of “Bang! You’re Dead” was generated by isolating 1s segments of the movie and arranging them in a pseudorandom order, thereby eliminating the temporal coherence of the narrative (Naci et al., 2014). To create the scrambled version of “Taken”, the audio was spectrally rotated, which preserved many of its acoustic features but rendered the speech indecipherable (Naci et al., 2015). The scrambled movie clips were presented before the intact versions for all patients and participants to prevent potential carry-over effects of the narrative.

Two separate groups of healthy volunteers were recruited for this study: 13 participants watched the intact and scrambled versions of “Bang! You’re Dead”, and 15 participants heard both versions of “Taken”. Individual participants were seated in a dimly lit room and instructed to watch or listen attentively to the stimuli. The task instructions and design remained the same when testing patients with DOC. Each patient was presented with one or both movie types (12 “Bang! You’re Dead”; ten “Taken”; nine both) with the presentation order counterbalanced between patients.

Stimulus presentation was controlled with the PsychoToolbox plugin for Matlab (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) on a 15” Apple MacBook Pro. The laptop screen was used to present the video component of “Bang! You’re Dead” but remained blank (black) during “Taken”. All audio was presented binaurally to participants at a
comfortable listening volume through Etymotics ER-1 in-ear headphones. The EEG data were analyzed using EEGLAB software (Delorme & Makeig, 2004). The data were cleaned following standard preprocessing steps including re-referencing, filtering, and removal of artifacts (e.g., ocular, motor). Finally, estimates of cortical activity during “Taken” were computed with the Brainstorm software for MATLAB (Tadel et al., 2011). Source reconstructions were performed only for “Taken” because of the availability of T1 structural MRI scans among participants in this condition.

2.2.3 EEG acquisition

EEG data were collected using a 129-channel cap (Electrical Geodesics Inc. [EGI], Oregon, USA). Signals were sampled at 250Hz and referenced online to the vertex (Cz). Electrode impedances were kept below 50kΩ. Offline processing was performed using MATLAB software, including custom scripts and the EEGLab toolbox (Delorme & Makeig, 2004). Offline, the EEG data were re-referenced to the common average and bandpass filtered from 0.5 - 60Hz (notch at 60Hz). Automatic artifact detection (EEGLAB) was used to identify bad channels, which were removed, then interpolated back into the data. We then used an independent components analysis (ICA) to visually identify patterns of neural activity characteristic of eye and muscle movements which were removed from the data. The data were also de-spiked to reduce the influence of aberrant peak amplitudes on further analyses (Dmochowski et al., 2012). EEG preprocessing was performed separately for each participant, movie, and stimulus condition.

2.2.4 Statistical analyses

We performed a correlated components analysis (CorrCA; Dmochowski et al., 2012; Ki et al., 2016) to calculate ISCs from the EEG data. CorrCA identifies linear combinations of stable and distinct patterns of brain activity to generate “components” that are maximally correlated (using Pearson’s rho) between participants (see Cohen and Parra, 2016; Ki et al., 2016 for calculations). Here, the components serve a similar purpose to those extracted from fMRI data using group-level ICA, in that they reflect common patterns of neural activity across participants. Since components derived by the CorrCA
are rank-ordered by the magnitude of their correlations, we focused on the top-ranked component for each movie condition.

A CorrCA was first computed in healthy controls for each movie (“Bang! You’re Dead” and “Taken”) and condition (intact, scrambled). In computing the CorrCA (Dmochowski et al., 2012; Ki et al., 2016), the spatial weights of the top component are back-projected onto the EEG recordings from individual participants, creating a spatial filter of the data, which isolates the underlying signal of the component and its activity over time. These per-subject component time courses are then correlated between all pairs of participants, and the mean of the pairwise correlations for each individual participant represents their overall ISCs; that is, how “synchronized” each participant is to the group as a whole.

Leave-one-out cross-validation and permutation testing were then used to determine the reliability of the components as well as evaluate the statistical significance of individual ISCs during each movie. The leave-one-out approach involved iteratively removing one participant from the group and recomputing the CorrCA (which generated new components), and the extracted time courses for each iteration of the CorrCA were later used to compute ISCs. That is, we repeated the CorrCA 13 times for “Bang! You’re Dead” and 15 times for “Taken”—leaving out a different participant during each recalculation—and computed ISCs between the left-out participant and the set of participants included in each iteration of the CorrCA. This also enabled us to compare the components topographies generated by the CorrCA across subsets of the group and measure the average degree of synchronization for each participant across these subsets. This approach ensured that the components extracted using CorrCA and the subsequent ISCs between participants were unbiased and reliable.

Permutation testing was then used to establish thresholds of statistical significance for the ISCs of individual participants. This was done by phase-shifting the correlation coefficients between participants (Dmochowski et al., 2012; Ki et al., 2016; Theiler et al., 1992) and performing a 1000 iteration resampling procedure to create individual null distributions. The top 5% of the distributions formed the significance thresholds for each participant ($p < 0.05$ FDR corrected). The leave-one-out and permutation analysis also
served as a statistical benchmark for assessing the extent to which individual DOC patients were synchronized to healthy controls during the movies. The analysis followed a similar procedure with one exception: rather than computing new CorrCA components using patient data, we back-projected the initial components from healthy controls onto their EEG. In this way, we could directly compare the neural activity from patients to the healthy group.

2.2.5 Suspense ratings and temporal inter-subject correlations

To verify that the component extracted by the CorrCA represented neural activity associated with executive processing of the plot (Dmochowski et al., 2012; Cohen and Parra, 2016, Poulsen et al., 2017), we examined whether the temporal fluctuations of ISCs coincided with subjective ratings of suspense during both movies. To do this, we first collected suspense ratings for “Bang! You’re Dead” and “Taken” from two independent samples of 20 healthy volunteers. Participants rated how much “suspense” they felt at 2s intervals throughout the movie, ranging from 1 (least) to 10 (most). Individual ratings were then averaged to create a group-level time course of suspense ratings specific to each movie. Second, we used a sliding window technique—set at 2s intervals to align with the sampling frequency of the suspense ratings—to identify time periods when the EEG activity from each participant was significantly correlated to the mean of the group (based on a leave-one-out approach). Significance was established against null distributions that were generated for each participant at every time window (2s) throughout the movie by randomly shuffling the component time course, recomputing the ISCs 1000 times, and retaining the value that corresponded to the 95th percentile. ISCs that exceeded this threshold at each time point were considered statistically significant. Group-level temporal ISCs were then calculated by summing the number of participants who were significantly synchronized to the group at every time point. Finally, we correlated the time course of the significant group-level temporal ISCs for each movie and condition (intact and scrambled versions) to the suspense ratings from the intact stimuli using both frequentist and Bayesian statistics.
2.2.6 Component source modelling

For those participants who listened to the “Taken” clip, we performed an exploratory source localization analysis using Brainstorm (Tadel et al., 2011) and a spatiotemporal regression (Custo et al., 2014) to uncover the potential cortical sources of the components. Head and cortical models were constructed using T1 weighted structural MRI images and automatic (OpenMEEG) boundary-element modelling (Gramfort et al., 2010; Mosher et al., 1999). To improve the accuracy of the source estimates, electrode placements were captured for each participant during EEG acquisition using EGI’s Geodesic Photogrammetry System and co-registered to their corresponding head models. Sources were reconstructed from full EEG recordings from healthy controls for the intact and scrambled versions of “Taken” using a Tikhonov-regularized weighted minimum norm estimate with normalized current density maps. Individual cortical models and source estimates were then normalized to MNI (Montreal Neurological Institute) standard space. A spatiotemporal regression analysis (Custo et al., 2014) was performed to identify cortical sources that correlate with the group-level component time courses for each version of “Taken”. We then repeated the regression using the auditory envelope of the stimulus. Significant beta maps (corrected for multiple comparisons) were exported to SPM (Statistical Parametric Mapping), where we computed group-level t contrasts between the intact (intact > scrambled) and scrambled (intact < scrambled) audio conditions. This yielded contrast maps of the significant differences in functional activity associated with the activity of the top components from the CorrCA.

2.3 Results

2.3.1 Neural synchronization during naturalistic audiovisual stimulation

For the intact version of “Bang! You’re Dead”, the CorrCA produced a component topography that showed extensive frontal negativity and widespread posterior positivity among healthy controls (Figure 1A). This component was remarkably reliable between smaller subsets of control participants (spatial correlations, r > 0.95; Figure 1B), as demonstrated by the leave-one-out recalculations of the CorrCA. In effect, we found
nearly identical patterns of neural activity each time we performed the CorrCA, irrespective of the participants included in the analysis; the group-level component for “Bang! You’re Dead” was not simply the product of the specific configuration of our sample but, rather, captured the most common neural response to watching this movie. The ISCs, likewise, showed a similar degree of reliability. At the group level, the mean ISCs during “Bang! You’re Dead” ($M = 0.084$, $SD = 0.053$) were significant, $t(12) = 5.700$, $p = 9.98e^{-5}$, confirming both that our task was generating inter-subject synchronization and that our EEG analyses could identify this synchrony. In fact, between individual participants, we found 85% whose EEG activity was significantly correlated to the rest of the group during “Bang! You’re Dead” ($p < 0.05$ FDR corrected; Figure 1C).

At the group level, the temporal ISCs showed a comparable degree of consistency. We found that the EEG from healthy controls were significantly synchronized at the same time points for 25.32% of the intact version of “Bang! You’re Dead” (based on permutation statistics). Moreover, the group-level synchronization at each time point was significantly correlated to the average suspense ratings throughout the intact movie, $r = 0.179$, $p = 6.00e^{-3}$, $BF_{10} = 3.541$. This revealed that individuals’ neural activity was most synchronized at times when the movie was most suspenseful, which suggested, therefore, that the top CorrCA component reflected executive processing of the movie (Cohen et al., 2017; Naci et al., 2014).

We then performed the CorrCA on the EEG data from the same 13 healthy controls during the scrambled version of “Bang! You’re Dead” to compare the degree of ISCs to the intact condition. The CorrCA produced a component that closely resembled the intact condition and was equally consistent across leave-one-out subsets (spatial correlations, $r > 0.95$). The group-level mean ISCs ($M = 0.071$, $SD = 0.032$) remained significant during the scrambled movie, $t(12) = 8.047$, $p = 3.54e^{-6}$. While this corresponded to previous fMRI studies (Naci et al., 2014, 2015), we tested whether the components calculated for each condition reflected similar underlying neural processes. To do this, we back-projected the intact and scrambled components onto the EEG data from the other movie condition (intact onto scrambled and scrambled onto intact) and recomputed the ISCs.
This produced a unique series of ISCs representing the overlap in neural processes captured by the components in both movie conditions. We predicted that if the components encompassed the same neural processes, the magnitude of the ISCs would remain largely unchanged. However, this was not the case. At the group level, we observed a significant reduction in group-level mean ISCs for both the intact, $t(12) = 3.640, p = 3.00e^{-3}$, and scrambled movie conditions, $t(12) = 2.659, p = 2.10e^{-2}$, which confirmed that, despite displaying similar levels of synchronization, the intact and scrambled components did not arise from the same underlying processes. As a follow-up, we ran a 2x2 factorial ANOVA to ensure that this effect was not driven by an interaction between the different movie conditions and the component projection type (i.e., correct or incorrect). The ANOVA confirmed a main effect of projection type, $F(1,12) = 20.83, p = 7.00e^{-4}$ but did not reveal a significant condition by projection type interaction, $F(1,12) = 0.73, p = 4.1e^{-1}$ (Supplementary Information Figure 1A).

The temporal ISCs revealed that, during the scrambled version of “Bang! You’re Dead”, participants’ EEG activity was significantly synchronized for 20.25% of the movie—5% less than the intact version (Supplementary Information Figure 2A, B). Although this reduction in significant temporal ISCs was markedly less pronounced than those reported by Dmochowski et al. (2012), the temporal ISCs for this condition did not correlate with the suspense ratings for the intact movie, $r = 0.045, p = 4.86e^{-1}$, BF$_{10} = 0.103$. What this suggests is that, although participants EEG activity was still synchronized to a comparable degree during the scrambled version of the movie, this was unrelated to the underlying elements of the plot, like its suspense (Naci et al., 2014).

Using the component from the intact movie condition, we then calculated ISCs for 12 DOC patients while they watched the intact version of “Bang! You’re Dead”. Overall, 25% of patients had EEG activity that was significantly correlated with healthy controls’ during this movie ($p < 0.05$ FDR corrected; Figure 1D), though the magnitude of their absolute correlations with controls was markedly lower on average. Notably, all of these patients met the behavioural criteria for a vegetative diagnosis at the time of testing. We repeated this procedure using the component topography for the scrambled version of the movie. Scrambled data were available for 10 of the 12 patients who watched “Bang!
You’re Dead!”. During the scrambled movie condition, 20% of individual DOC patients’ neural activity was significantly synchronized with controls ($p < 0.05$ FDR corrected). While there were a similar number of patients whose neural activity was significantly correlated with controls’ during either the intact or scrambled condition, there was no overlap between these patients. Interestingly, the ISCs for three patients increased during the scrambled movie condition, though the increases for two were comparatively small relative to the intact condition.

2.3.2 Neural synchronization during naturalistic auditory stimulation

We applied the same CorrCA procedure to the EEG data from 15 different healthy controls while they listened to the intact version of “Taken”. The topography of the intact component showed a posterior negativity and widespread frontal positivity that was spatially analogous to the intact component from “Bang! You’re Dead” (Figure 2A). However, this component was much less stable across leave-one-out subsets (spatial correlations, $r > 0.67$). Nevertheless, group-level mean ISCs ($M = 0.019$, $SD = 0.009$), remained significant, $t(14) = 8.417$, $p = 7.55e-7$, though reduced compared to “Bang! You’re Dead”, likely owing to the unimodal nature of the clip.

The group-level temporal ISCs showed that participants’ EEG activity was significantly synchronized throughout 15.79% of the audio and that these periods of synchronization were significantly correlated with its suspense ratings, $r = 0.186$, $p = 2.00e-1$, $BF_{10} = 1.245$. Like “Bang! You’re Dead”, this result indicated that the EEG activity was maximally synchronized at the group level during the most suspenseful points of the audio clip from “Taken”.

For the scrambled version of “Taken”, the CorrCA produced a component that differed considerably from the intact version and from either of the components calculated on the “Bang! You’re Dead” data (see Suppletory Information Figure 3 for topographies).
Figure 1. Component topographies and inter-subject correlations during “Bang! You’re Dead”.

A) The spatial weights that maximize Pearson’s correlation (r) between healthy controls during the intact version of “Bang! You’re Dead”. B) The similarity matrix and polarity-normalized component topographies computed from iterative leave-one-out recalculations of the CorrCA. Spatial correlations are plotted across the scalp topographies, rather than the typical voltage mappings. Warmer colours indicate higher r values. C) Mean inter-subject correlations between healthy controls during the intact version of “Bang! You’re Dead”. Statistical thresholds (blue dashes) were calculated on a per-subject basis using a permutation test approach. D) Mean inter-subject correlations between individual patients and the healthy control group during the intact version of “Bang! You’re Dead”. Statistical thresholds (red/green) were determined on an individual basis for each patient using a permutation approach. Green thresholds and asterisks denote significance at p < 0.05. E) The distribution of ISCs for control participants (blue) and three patients who were significantly correlated to the healthy group (red) during “Bang! You’re Dead”.

This component was the least consistent between leave-one-out subsets (spatial correlations, minimum r = -0.44), though group-level mean ISCs (M = 0.016, SD =
0.009) were significant, $t(14) = 7.073, p = 2.00e-1$. However, like “Bang! You’re Dead”, the recalculation of the group-level ISCs after back-projection revealed that the neural activity underlying these components differed between conditions; we found significant reductions in ISCs for the intact condition after back-projecting the scrambled component, $t(14) = 6.901, p = 7.28e-6$ and, likewise, for the scrambled condition after back-projecting the intact component, $t(14) = 5.612, p = 6.40e-5$. Like “Bang! You’re Dead”, a 2x2 factorial ANOVA revealed a main effect of projection type, $F(1,14) = 73.12, p = 6.30e-7$, but no significant interaction between the variable, $F(1,14) = 2.04, p = 1.75e-1$ (Suppletory Information Figure 1B.)

For the group-level temporal ISCs, we found that participants neural activity synchronized during only 9.87% of the scrambled version of “Taken”. Moreover, like the scrambled version of “Bang! You’re Dead”, the temporal ISCs did not correlate with the suspense ratings from the intact version of “Taken”, $r = 0.107, p = 2.00e-1$, BF$_{10} = 0.233$, suggesting again that synchronization among participants in this condition was not plot-based (Suppletory Information Figure 4 A, B).

With the component from the intact version of “Taken”, we calculated the ISCs between ten patients with DOC and the healthy control group. Here, we found that 30% of patients produced EEG activity that was significantly correlated with controls during this movie (Figure 2B). Of these patients, one was diagnosed with Locked-in Syndrome (Table 1), while the remaining patients met the behavioural criteria for a vegetative state diagnosis. EEG data from the scrambled audio condition was available for 9 of the 10 patients who listened to the intact version of “Taken”. Here, two of the nine patients showed increased ISCs with controls relative to the intact condition. Nevertheless, following the same back-projection procedure, we did not find significant correlations between the EEG activity of any DOC patients and healthy controls during this condition.
Figure 2. Component topographies for both movie conditions and inter-subject synchronization between patients and controls during “Taken”.

A) Maximally correlated components calculated between healthy controls during the intact versions of “Bang! You’re Dead” (left) and “Taken” (middle), shown for comparison. Mean inter-subject correlations between individual patients and the healthy control group during the intact version of “Taken”. Statistical thresholds (red/green) were determined on an individual basis for each patient using a permutation approach. Green thresholds and asterisks denote significance at $p < 0.05$. B) The distribution of ISCs for control participants (blue) and three patients who were significantly correlated to the control group (red) during “Taken”.

2.3.3 Source localization

Finally, we performed a source localization analysis on the healthy control data from both versions of “Taken” to investigate the neural generators of the components. Paired $t$ contrasts were calculated on the cortical activations that most strongly correlated with the time courses of the intact and scrambled components. This revealed a significant difference in overall activation between movie conditions (SPM paired $t$ contrasts at $p < .05$). The intact > scrambled contrast showed greater bilateral activation over frontal and parietal regions (Figure 3A), whereas the scrambled > intact contrast revealed only sparse activation over anterior regions of the inferior and middle temporal cortices (Figure 3B). Despite the exploratory nature of this analysis, the differences in cortical activity between movie conditions closely resembled previous findings in fMRI (Naci et al., 2014, 2015).

To ensure that these results did not simply reflect differences in the auditory characteristics between the intact and scrambled movie, we performed a follow-up analysis to identify the brain areas associated with processing the low-level auditory
properties of “Taken”. Specifically, we contrasted the cortical response to the physical features of the intact audio (i.e., its pitch, timbre, and loudness—captured by its auditory envelope) to the activity elicited by the full audio clip (containing speech and the plot). We performed paired $t$ contrasts between the intact audio > auditory envelope and auditory envelope > intact audio and found that there was a significant difference between the overall source activations for each condition, $t(14) = 3.79, p = 1.00 \times 10^{-3}$.

Moreover, the difference maps between contrasts bore a considerable resemblance to the intact > scrambled localization analysis. From these analyses, we, therefore, concluded that neither the auditory envelope of the intact version of “Taken”, nor the perceptual features of the scrambled movie generated the frontoparietal activation observed during the intact audio condition.

![Source reconstruction of the top CorrCA components for the intact and scrambled versions of “Taken”.](image)

**Figure 3.** Source reconstruction of the top CorrCA components for the intact and scrambled versions of “Taken”.

A) Source activations that were significantly correlated with the component time course from the intact version of “Taken” contrasted against the activity from the scrambled condition (intact > scrambled). B) Source activations that were significantly correlated
with the component time course from the scrambled version of “Taken” contrasted against the activity from the intact condition (intact < scrambled).

2.4 Discussion

Overall, we found that the EEG responses of 38% of DOC patients (four vegetative, one Locked-in) in this cohort were significantly correlated to those of healthy controls during at least one of our movie clips. This result suggests that these patients may have retained or recovered some of the “executive” faculties necessary for processing the plot of the movie stimuli we used (Naci et al., 2014, 2015). This percentage (38%), is higher than previous studies that have used neuroimaging and covert command-following (14% of vegetative patients, 32% of minimally conscious patients; Kondziella et al., 2016). This potentially speaks to the simplicity of our movie paradigm, as well as the inherent ease with which we attend to engaging movie stimuli (Dmochowski et al., 2014; Hasson et al., 2004; Ki et al., 2016; Naci et al., 2015). However, the percentages reported here reflect findings across a small cohort of DOC patients and should be interpreted with caution when compared to the larger body of literature. Repeat testing and validation among a larger sample of DOC patients would be needed before the proportion of cognitively capable DOC patients reported in this study could be appropriately applied to the population as a whole.

Although it is challenging to infer the cognitive states of DOC patients from these results alone, significant correlations in neural activity between these patients and healthy controls during our movie tasks suggest that they may have been having a comparable experience of the plot for a number of reasons. In particular, the results from our analysis of our healthy control data align with previous studies (in both component topography and the magnitude of ISCs) that used CorrCA to examine the neural processes of engagement associated with movie-watching (Cohen & Parra, 2016; Dmochowski et al., 2012; Ki et al., 2016; Poulsen et al., 2017) and, importantly, with those of a recent investigation of the electrophysiological markers of auditory attention in DOC patients (Iotzov et al., 2017). In that study, Iotzov et al. recorded EEG activity from patients with DOC while they listened to a spoken narrative and compared their responses to that of
healthy controls on three components derived from a CorrCA. At the group level, Iotzov et al. observed a significant reduction in ISCs for DOC patients compared to control across all three components and found some evidence that the magnitude of ISCs corresponded to clinical diagnosis. We also performed three additional analyses to disentangle the ISCs generated from the sensory properties of the movies from those driven by the plot. First, we back-projected the components from the intact and scrambled movies onto the EEG data from the other movie condition (intact onto scrambled, scrambled onto intact). This created a spatial filter that isolated the neural signal of the intact component in the scrambled EEG data and vice versa. Had the components for each condition captured the same neural processes, we would have expected no change in the ISCs. However, using this method, we found consistent and significant decreases in mean ISCs for both “Bang! You’re Dead” and “Taken”. The reduction in mean ISCs demonstrated that the components from each movie condition encompassed different neural processes.

We then compared the time course of inter-subject synchronization, computed using temporal ISCs, with the suspense ratings for each movie. We found that participants were maximally synchronized during time windows that corresponded to the most suspenseful periods of each movie but only during the intact (and not the scrambled) conditions. This provided further evidence that the components calculated for the intact version of the movies represented brain activity associated with executive processing necessary to track the narrative, rather than the sensory properties, of the movies. Lastly, the source reconstruction of the components from “Taken” revealed a clear separation between the brain regions involved in processing the intact and scrambled versions of the movie. That is, the intact component was localized primarily to the frontoparietal cortices, whereas the scrambled component activity was localized largely to temporal auditory regions, aligning closely to results shown in fMRI (Hasson et al., 2004; Naci et al., 2014, 2015). This suggests patients are recruiting the same set of executive processes (i.e., attention, language processing, memory, and theory of mind; Naci et al., 2014; Cohen and Parra, 2016; Ki et al., 2016) that are essential for plot following.
How do we know that synchronization between DOC patients and healthy controls is not the result of some kind of automatic or unconscious processing? While previous studies on the neural effects of anesthesia have shown that inter-subject neural synchronization can occur in low-level brain areas in the absence of awareness (Naci et al., 2018), we contend that automatic or unconscious processing alone cannot explain significant ISCs during the intact movies in our study. Indeed, the source results for the intact and scrambled “Taken” components share the same distinct activation patterns found in similar fMRI paradigms (Naci et al., 2014, 2015). Frontoparietal synchronization has been shown to correlate strongly with higher-order elements of movie stimuli, like its plot, which cannot be processed unconsciously (Naci et al., 2018). Furthermore, if ISCs during the intact movie conditions were primarily sensory-driven, we would expect the components to index the same neural processes as the scrambled components. Our back-projection analysis determined that this was not the case, despite the sensory properties of the stimuli being largely the same between conditions. Finally, inter-subject neural synchronization is not a natural state of the brain; it does not occur when participants are at rest (Hasson et al., 2004; Naci et al., 2014) and is much weaker in the absence of focused attention (Ki et al., 2016) or during non-engaging stimuli (Dmochowski et al., 2012; Hasson et al., 2010).

There are some peculiarities in our patient results that should be addressed. First, the majority of DOC patients who had significant ISCs with healthy controls were behaviourally vegetative, not minimally conscious. One factor that may account for this result relates to data quality; EEG is very susceptible to movement artifacts, which may have been more prevalent for the minimally conscious patients (who are more likely to move overall), potentially impacting their ISCs with the healthy group. Similarly, some percentage of vegetative patients are likely to be covertly aware but simply cannot express this through their behaviour, whereas minimally conscious patients are, as their diagnosis suggests, minimally conscious and therefore have limited cognitive, as well as behavioural capacities. As a result, patients who are behaviourally vegetative but fully aware would be expected to process movie stimuli similarly to healthy controls, while
patients who are minimally conscious may experience more difficulties, lowering their overall ISCs with controls.

A second notable finding comes from the patient ISCs during the scrambled conditions; the two patients who were significantly synchronized with the control group during the scrambled version of “Bang! You’re Dead” were not synchronized with the control group during the intact condition. A possible explanation for these results is that the two patients who were synchronized with controls during the scrambled version retained some cognitive or attentional resources and were minimally engaged while it played. This is possible because the scrambled version of “Bang! You’re Dead” contained some residual structure. However, the neural activity from these patients was not significantly synchronized during in the intact version of the movie, perhaps due to fatigue (the intact movie was presented after the scrambled version), or disinterest. This itself is not unusual; even among the healthy control group, one participant whose EEG was synchronized with the rest of the control group during the scrambled version of the movie was not significantly synchronized during the intact version. Such findings speak to the inherent variability associated with measures designed to assess individual cases. This provides added motivation for evaluating the reliability of this method for determining residual cognitive processing in the patients with DOC, ideally by conducting longitudinal studies whereby repeated measures are taken.

Overall, 38% of patients tested were significantly synchronized with healthy controls during either “Bang! You’re Dead” or “Taken”. However, among these patients, only one (Patient 10, see Table 1) showed significant ISCs with controls during both movies (of the nine who were tested with both). While significant synchronization during both movies provides the strongest evidence of residual processing, inconsistencies in ISCs between movie types for most patients underscores the need for a holistic testing approach that employs multiple tasks to identify covert cognitive processing in this population (Engemann et al., 2018; Gibson et al., 2014; Kirschner et al., 2015; Sitt et al., 2014). Individual patients with DOC likely have marked differences in sensory and cognitive function, and brain-based assessments should be designed with this in mind.
The results of this study set the stage for developing sensitive and reliable brain-based assessments of covert cognitive processing and, potentially, awareness in patients with DOC—ideally, ones that can be administered easily in clinical settings. The paradigm presented here moves one step closer to achieving this goal. By developing a bedside EEG movie task (Naci et al., 2014, 2015), we were able to quantify a neural index of cognitive processing while simultaneously minimizing the physical burden to patients incurred during fMRI testing. Likewise, the majority of EEG tasks used to assess cognitive function and awareness in DOC patients to date have done so by examining changes in neural activity that are either elicited automatically (e.g., event-related potentials; Kotchoubey et al., 2005) or depend upon active responding (Cruse et al., 2011, 2012). In both contexts, these paradigms are often contrived or unnatural, making an already difficult task even more challenging. Furthermore, the event-related approaches routinely used for clinical neurological assessments require hundreds of trials to open a brief window into the sensory and cognitive function of DOC patients; whereas our method was specifically developed to work with a single sample of continuous EEG, recorded during a short naturalistic movie task, to assess covert cognition in individual patients with DOC.

For any task to be included in the standard clinical assessment repertoire, it must be rapid and allow for individual assessments of cognition at the bedside without the need for complex tasks or instructions. Our paradigm meets all of those requirements. Taking cues from continuous clinical monitoring and brain-computer interfaces (Abdalmalak et al., 2017; Chatelle et al., 2012; Laureys et al., 2005; Naci et al., 2012), the future of the CorrCA method could allow for examination of moment-to-moment ISCs between DOC patients and controls during movie tasks, further supplementing behavioural measures of awareness at the bedside.
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Chapter 3

3 A comparison of English and French naturalistic listening paradigms for the assessment of consciousness in unresponsive individuals

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https://doi.org/10.1109/SMC42975.2020.9283263

3.1 Introduction

Severe brain injury is a medical emergency requiring immediate hospitalization and critical care intervention. Fortunately, continued advancements in intensive medicine have improved the likelihood of survival from serious brain injury, but recovery in the short and long term remain difficult to predict. Patients in critical care will routinely undergo a battery of behavioural assessments and continuous neurological monitoring to establish baseline levels of reactivity and neuronal function. However, preserved awareness in the acute stages of severe brain injury is challenging to infer from standard clinical measures alone. Specialized neural assessments that use advanced neuroimaging technologies like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) may provide deeper insights into the cognitive state of patients with acute brain injury, which may have significant implications for medical management and prognostication (Andrews et al., 1996; Childs et al., 1993). In fact, recent developments in the study of disorders of consciousness (DoC) suggest that advanced neural assessments may be crucial in this regard (Owen, 2013).
DoC are a classification of neurological disorders that can result from serious brain injury. After recovery from coma, DoC present as a state of apparent wakefulness with impaired conscious awareness (Bernat, 2006; Laureys et al., 2004; Owen, 2008) and are diagnosed using behavioural measures like the Coma Recovery Scale-Revised (CRS-R; Kalmar & Giacino, 2005). Patients who remain awake, but behaviourally non-responsive during CRS-R assessment meet the clinical criteria for the vegetative state (also known as unresponsive wakefulness syndrome; UWS), and are presumed to be entirely unaware; that is, unaware of who they are, where they are and the predicament they are in. In contrast, patients who exhibit inconsistent but reproducible evidence of awareness are typically diagnosed as being in a “minimally conscious state”. However, a lack of consistent responding during behavioural assessment could be indicative of any number of cognitive or motor impairments that are unrelated to a patient’s conscious state—the latter of which is evidenced by patients diagnosed with Locked-in Syndrome (LIS) who remain fully aware but largely unable to speak or move (Laureys et al., 2005). As such, over a decade ago, researchers began to investigate the utility of using neuroimaging as a more sensitive means of assessing awareness in DoC.

In 2006, Owen et al. (Owen et al., 2006) first reported unequivocal evidence that some patients with DoC are, in fact, entirely aware. In that study, Owen et al. (Owen et al., 2006) used fMRI and two mental imagery paradigms to assess “covert” command-following—responding through neural activity rather than behaviour—in one patient who was, by all clinical accounts, in a vegetative state. They found clear, consistent, and sustained activation in regions of the brain associated with each imagery condition that were statistically indistinguishable from those observed in healthy controls. These findings were later replicated in a larger cohort of patients with DoC (Monti et al., 2010), while multiple similar neuroimaging tasks have since been developed to index awareness, as well as different dimensions of residual cognition using fMRI and EEG (Cruse et al., 2011; Naci et al., 2014).

More recent years have seen a shift away from “active” task-based approaches to assessing awareness in DoC, and towards more naturalistic paradigms that approximate real-world contexts, like watching movies or listening to stories. Movie-watching, in
particular, has emerged as a rapid and more ecologically-valid approach to assessing awareness in DoC patients. The multi-dimensional nature of movies, in that they contain visual information, sound, speech, and most importantly, a narrative, makes them ideal for assessing cognitive function and covert awareness. For example, a study by Naci et al. (Naci et al., 2014) leveraged a phenomenon called inter-subject neural synchronization to assess higher-order “executive” processing in patients with DoC. When individuals watch the same movie in an fMRI scanner (or while wearing a functional near-infrared spectroscopy cap; Liu et al., 2017), their brains tend to “synchronize”, that is, voxel-wise activity across participants becomes highly correlated (Hasson et al., 2004). This effect is particularly pronounced when the movies are highly engaging or suspenseful. Naci et al. (Naci et al., 2014) capitalized on this neural synchronization and designed an fMRI paradigm to assess the degree to which patients with DoC synchronized to healthy controls during a short, suspenseful Alfred Hitchcock movie called “Bang! You’re Dead”. They observed significant brain-wide synchronization among controls, including in frontoparietal regions that are responsible for higher-order executive functions such as attention, working memory and theory of mind (Ptak, 2012; Wolinski et al., 2018; Yeshurun et al., 2017). Moreover, they found that synchronization between participants in these frontal and parietal areas correlated with independent subjective and objective ratings of suspense during the movie, acquired from separate groups of participants tested outside the scanner. When they tested two patients with DoC using this paradigm, they found that the frontoparietal activity in one patient was significantly correlated with the healthy group, providing strong evidence that they were processing the higher-order elements of the movie, like its plot. On this basis, the authors concluded that the patient was consciously aware (Naci et al., 2014), and this was later independently verified using alternate neuroimaging approaches.

While considerable progress has been made in developing reliable neural assessments of awareness and cognitive function in DoC, the use of these paradigms to assess covert awareness in acutely brain-injured patients has only just begun to be explored (Claassen, et al., 2019; Edlow et al., 2017). In this study, we developed an EEG protocol to index inter-subject neural synchronization (inter-subject correlations, ISCs) among healthy
controls during an auditory movie task (Dmochowski et al., 2012; Ki et al., 2016).

Compared to fMRI, EEG is low-cost and portable, which makes it ideally suited for bedside assessment of patients in critical care. Additionally, to maximize the applicability of this protocol in the Canadian context, we compared two versions of the same audio clip, one English and one French, to determine whether this task could be used in both English and French-speaking individuals and, if so, to establish baseline measures of ISCs from healthy controls in both languages. To accomplish this, we tested three main hypotheses. First, we hypothesized that the “Taken” stimuli would produce significant ISCs between participants, irrespective of language and that we could detect this using EEG (Dmochowski et al., 2012; Ki et al., 2016). Second, we predicted that the narrative of “Taken” would recruit areas of the frontoparietal “executive” network, resulting in higher ISCs across groups compared to a scrambled control version of the same audio (Naci et al., 2014, 2015). Third, we hypothesized that if neural synchronization is driven in large part by the plot of “Taken”—which unfolds the same way in both English and French—the ISCs would correlate over time between the two languages. This would provide strong evidence, not only that the same executive processes are involved in English and French narrative processing, but that these measures are indexing brain processes that are specifically related to plot-following, rather than some other (e.g. sensory) properties of the narrative stream (Dmochowski et al., 2012; Naci et al., 2014, 2015).

3.2 Methods

3.2.1 Participants

Ethics approval for this study was granted by the institutional research ethics boards at the University of Western Ontario and McGill University (Appendix A). Thirty-four participants were enrolled in this study: we recruited twenty participants from the Brain and Mind Institute at the University of Western Ontario—eighteen English-speakers and two English-French bilinguals—and fourteen participants from a research subject pool at McGill University. Eighteen native English-speaking participants listened to the English versions of the stimuli, and sixteen native French-speaking participants listened to the
French versions. All participants had self-reported normal hearing. Another 20 participants were recruited from the University of Western Ontario during an earlier study to perform a behavioural suspense ratings task while listening to the intact English version of “Taken”. Written informed consent was obtained prior to testing, and participants were compensated for their time.

3.2.2 Stimuli and experimental procedures

For this study, we used English and French versions of a short (5 minute) suspenseful auditory excerpt from the movie “Taken”. We chose to use auditory stimuli rather than an audio-visual clip like “Bang! You’re Dead” to account for likely visual impairments in many patients with acute brain injury. The content of this clip has been described in detail elsewhere (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015). Briefly, it depicts a tense phone conversation between a father and his daughter, who, with instructions from her father, is attempting to hide from intruders in her accommodations. Like “Bang! You’re Dead”, this clip is highly suspenseful and produces reliable frontoparietal synchronization in healthy volunteers when tested with fMRI (Naci et al., 2015). Notably, although the English and French versions of the clip depict the same overall narrative, the timing with which events occur is not identical. In addition to any differences in speech pacing between the two languages, the English version contains a nearly 10s delay early on in the clip that occurs prior to the start of the conversation between the father and daughter. In these 10s, listeners can hear the daughter’s phone ringing, but the sound is being drowned out by her playing loud rock music. This scene is much shorter in the French version of the clip. The 10s lag remains constant for the remainder of the English clip. Nevertheless, the EEG activity was epoched at the same time points and encapsulated the entire duration of the narrative for both English and French versions.

We also used “scrambled” versions of the two audio clips to serve as perceptual control conditions in this study. The scrambled stimuli were generated using two techniques: spectral rotation and temporally reversing the audio. The intact and scrambled English versions of “Taken” were from an earlier study that had used spectral rotation to scramble the audio. This scrambling procedure preserved the auditory properties of the stimuli but
rendered the speech, and therefore the narrative, indecipherable (Naci et al., 2015). The French-language clips were generated specifically for this study. Here, we scrambled the audio by temporally reversing the intact version of “Taken” to investigate whether the presence of speech sounds in scrambled stimuli affected ISCs (Lerner et al., 2011). Although the scrambling techniques were different, both effectively removed the narrative from the clip and allowed us to compare the neural activity associated with auditory processing from that underlying plot-following specifically. Stimulus presentation was controlled by the Psychtoolbox (Kleiner et al., 2007) plugin for MATLAB running on a 15” Apple MacBook Pro, and audio was presented binaurally through Etymotics ER-1 in-ear headphones.

Participants were instructed to sit comfortably with their eyes open during the study and asked to listen attentively to the stimuli. We then presented the scrambled version of “Taken”, followed by the intact audio in either English or French depending on the participants’ spoken (native) language. This order of presentation was intended to minimize potential carry-over effects from the narrative in one condition to that in the subsequent condition. During the suspense ratings task, participants listened to the intact English version of “Taken” and were asked to rate how much suspense they felt at 2s intervals on a scale from 1 (least) to 10 (most). Responses were collected using a laptop keyboard while participants listened to the clip.

3.2.3 EEG data collection and preprocessing

EEG data were acquired using a 129-electrode saline-electrolyte sensor net connected to a Net Amps amplifier. Signals were sampled at 250Hz and referenced online to the vertex (Cz). Electrode impedances were kept below 50kΩ for the duration of the experiment. Offline preprocessing was performed using MATLAB software, custom scripts, and the EEGLAB toolbox (Delorme & Makeig, 2004). The EEG data were re-referenced offline to the common average and bandpass filtered from 0.5 - 60Hz, with a notch at 60Hz to remove line noise. We used a custom automatic artifact detection pipeline to identify bad channels, which we removed, then interpolated back into the data. Independent components analysis (ICA) was also used to identify patterns of EEG activity.
characteristic of eye and muscle movement. The ICA components were visually inspected, and those capturing artifacts were manually removed from the data. Finally, preprocessed EEG signals were de-spiked to reduce the influence of deviant peak amplitudes on later analyses (Dmochowski et al., 2012). EEG preprocessing was performed separately for each participant and condition.

3.2.4 Data analysis

We used a correlated components analysis (CorrCA) to identify patterns of EEG activity that were common across all participants during the tasks. CorrCA is a variant of a principal components analysis (PCA) that calculates the spatial weights of voltage activity across the scalp such that the activity is maximally correlated between subjects. The weightings are then used to extract discrete patterns of neural activity, or components, from the EEG that are highly correlated between subjects. Like PCA, CorrCA computes an eigenvalue decomposition of covariance data. However, CorrCA uses the pooled within-subject cross-covariance

\[ R_w = \frac{1}{N} \sum_{k=1}^{N} R_{kk} \]

and pooled between-subjects cross-covariance

\[ R_b = \frac{1}{N(N-1)} \sum_{k=1}^{N} \sum_{l=1, l \neq k}^{N} R_{kl} \]

where

\[ R_{kl} = \sum_t (x_k(t) - \bar{x}_k) (x_l(t) - \bar{x}_l)^T \]

calculates the cross-covariance between participant \( k \) and participant \( l \) across all electrodes at time \( t \) as the source of its covariance. The eigenvectors \( w_i \) of the cross-covariance matrix \( R_w^{-1}R_b \) with the largest eigenvalues \( \lambda_i \) calculated as \( (R_w^{-1}R_b)w_i = \lambda_i w_i \) are the components that maximize Pearson’s correlation between subjects in the data. The resulting \( N - 1 \) components, where \( N \) is the total number of sources—electrodes in this case—are then ranked-ordered by the overall strength of their correlations between subjects (Dmochowski et al., 2012; Ki et al., 2016). The spatial weights and time courses...
of these components, therefore, represent common patterns of neural activity across participants. We performed the CorrCA separately for each audio condition, and only the top-ranked components were used for later analyses.

3.2.5 Inter-subject correlations

To calculate ISCs, we first back-projected the component vectors \( w_i \) onto the EEG data from each participant. The back-projection created a spatial filter of the data, which isolated the time course of component activity for each subject. We then correlated these component time courses (using Pearson’s rho) between participants and calculated the average correlation between each subject and the rest of the group. These average correlations represented the individual subject ISCs. Finally, t-contrasts were performed on the mean ISCs across the groups to compare the degree of synchronization between stimulus conditions.

Although this approach captured the overall degree of inter-subject neural synchronization during the “Taken” task, it collapses across a crucial dimension of the narrative: its plot. One of the unique aspects of naturalistic stimuli like movies is that the plot unfolds over time, and plot elements like tension or suspense build gradually rather than being constant. In this sense, ISCs computed across the entire duration of the stimuli likely dampen the neural activity associated with plot-following over time. To this end, we capitalized on the temporal resolution of EEG and calculated ISCs in a time-resolved fashion using a sliding-window technique. Temporal inter-subject correlations (tISCs) were computed as the mean ISCs across participants within a 5s window with 3s of overlap. This resulted in new ISCs at 2s time intervals for the duration of the audio, which aligns with the repetition time (TR) of earlier studies investigating ISCs with fMRI (Naci et al., 2014, 2015). Statistical significance of the tISCs at each 2s time point was tested using permutation statistics. This approach involved shifting the phase of the correlations and using a 1000 iteration resampling procedure to generate null distributions of ISCs at each time point, with the top 5% of values representing the significance threshold (FDR corrected). A Chi-squared test of proportion was calculated...
to compare the number of time windows with significant ISCs between the intact and scrambled audio conditions

We also explored the 10s difference between the tSCs of the English and French versions of “Taken” using a cross-correlation analysis. We predicted that the offset of the narratives would likely have influenced the temporal structure of the tSCs time course and, therefore, the comparison between languages. The cross-correlation procedure iteratively shifted the tSCs for each condition to different time lags (5 lags in each direction, reflecting 10s shift in each direction) and allowed us to investigate the effect of the narrative offset between languages on the tSCs.

Finally, Pearson’s correlations were calculated between the tSCs for each condition and subjective ratings of suspense for the English version of “Taken” that were previously collected from an independent sample (N = 20). Here, participants were asked to rate how much “suspense” they felt on a scale from 1 - 10 (least to most) at 2s intervals during the intact version of “Taken”. The mean suspense ratings were then calculated for each time point and Z-normalized to generate an averaged “suspensefulness” time course. Despite only being collected for the English version of “Taken”, we predicted that the suspense ratings—which captured elements of the narrative beyond its purely linguistic properties—would correlate with the time course of ISCs for both English and French groups.

3.3 Results

3.3.1 Comparable inter-subject correlations across stimulus languages

The EEG data from three participants in the English group and five in the French group were excluded for excessive or systematic noise contamination. All further analyses were performed on 15 and 11 participants in the English and French groups, respectively. We first calculated the CorrCA on the intact and scrambled audio from the English language conditions. The component topographies (Figure 1a,c) bore some spatial similarities, with a clear anterior-posterior divide, but the overall voltage maps differed considerably between conditions. We then calculated the ISCs between the component time courses
for all participants for the intact and scrambled audio conditions. In line with our first hypothesis, we found that both the intact ($M = 0.015$, $SD = 0.006$) and the scrambled ($M = 0.012$, $SD = 0.006$) audio conditions produced significant ISCs at the group level, $t_{Intact}(14) = 9.60, p = 1.788e-07$, $t_{Scrambled}(14) = 7.22, p = 4.47e-06$, relative to the null hypothesis that no synchronization occurred during these conditions. When we compared the average ISCs between the intact and scrambled conditions, we found significantly higher ISCs for the intact condition, $t_{Intact-Scrambled}(14) = 2.24, p = 0.042$.

We then calculated the CorrCA and ISCs for the intact and scrambled French versions of “Taken”. The component topographies for the French audio conditions were largely dissimilar to those observed for the English language condition (Figure 1b,d) but the magnitude of the intact ($M = 0.019$, $SD = 0.007$) and scrambled ($M = 0.019$, $SD = 0.008$) versions were comparable. Likewise, both conditions produced significant ISCs across the group, $t_{Intact}(10) = 8.93, p = 4.411e-06$, $t_{Scrambled}(10) = 8.26, p = 8.88e-06$. However, unlike the English condition, the intact and scrambled ISCs were not significantly different in the French group, $t_{Intact-scrambled}(10) = -0.28, p = 0.78$. In fact, both the intact and scrambled versions of the French audio produced significantly higher ISCs than the scrambled English condition, $t_{FrenchIntact-EnglishScrambled}(24) = 2.74, p = 0.011$; $t_{FrenchScrambled-EnglishScrambled}(24) = 2.85, p = 0.009$.

### 3.3.2 Temporal inter-subject correlations reveal strong effect of plot

The ISCs demonstrated that each of the stimulus conditions produced significant synchronization across the group, but the effect of the plot was inconsistent between languages. We investigated the temporal dynamics of inter-subject synchronization using tISCs calculated at 2s time intervals throughout each audio condition. During the intact English version of “Taken”, the tISCs reached significance for 21.71% of the audio, compared to only 6.58% during the scrambled version. Similarly, significant tISCs occurred more frequently for the intact French version of “Taken”, occurring for 28.95% of the audio, compared to the scrambled French condition where significant tISCs were observed for only 9.21% of the audio (Figure 2a-d). The frequency of the tISCs for both languages was significantly higher during the intact audio condition compared to their
respective scrambled conditions, $\chi^2_{\text{English}}(1, N = 152) = 8.92, p = 0.003$, $\chi^2_{\text{French}}(1, N = 152) = 11.68, p = 6.327e^{-04}$, which suggested that the narrative was a significant factor driving inter-subject synchronization (rather than, say, the basic sensory properties of the intact and scrambled stimuli which were matched). We did not find any differences between the frequency of significant tISCs within conditions (i.e., intact to intact, scrambled to scrambled) between languages.

![Figure 4](image)

**Figure 4.** Component topographies and individual ISCs for the intact (top) and scrambled (bottom) versions of “Taken” across languages.

Group-level mean ISCs were comparable across the intact English ($M = 0.015, SD = 0.006$; A) and French ($M = 0.019, SD = 0.007$; B) audio conditions and both were significantly higher than the mean ISCs for the scrambled English version of “Taken” ($M = 0.012, SD = 0.006$; C). Interestingly, the mean ISCs for the scrambled French version of “Taken” ($M = 0.019, SD = 0.008$; D) did not differ significantly from the intact audio conditions.

We then directly compared the time courses of the tISCs between each audio condition. Despite having similar frequencies of significant synchronization, the tISCs between the intact English and French audio were not significantly correlated $r_{\text{English-French}}(24) = 0.05, p = 0.534$, nor were the tISCs between either language or audio condition. Additionally,
we compared the tISCs for the English and French versions of “Taken” to its suspense ratings. We found that the tISCs for the intact English audio were significantly correlated to the suspense ratings for “Taken”, $r_{\text{IntactEnglish}}(33) = 0.23, p = 0.005$. but the correlation between the intact French tISCs and suspense only approached significance, $r_{\text{IntactFrench}}(29) = 0.141, p = 0.09$. Neither of the scrambled tISCs were significantly correlated with the suspense ratings.

Overall, these results provided strong support for our second hypothesis that the ISCs were driven in large part by the narrative of “Taken”; the quantitative comparison of the significant tISCs over time suggested that participants were synchronized significantly more often throughout the intact audio conditions compared to the scrambled. This was further underscored by our finding that the tISCs from the English version of “Taken” were more highly correlated with the suspense ratings (acquired using the same English version) than were the tISCs from the French version. From the results presented here, we concluded that both the English and French narratives of “Taken” systematically recruited additional executive areas of the brain across participants(Hasson et al., 2004; Naci et al., 2014, 2015), and that these were closely associated with following its plot. This resulted in significant tISCs more frequently than in the scrambled versions.

### 3.3.3 Re-alignment of temporal inter-subject correlations accounts for narrative offset

The correlation between the intact English and French tISCs was unexpectedly low, given their comparable degree of overall synchronization (ISCs; Figure 1) and over time (tISCs; Figure 2). However, the 10s offset between the English and French narratives may have differentially affected the temporal properties of the tISCs, resulting in a lag between time courses. We explored this possibility using a cross-correlation analysis, which iteratively computed the correlations between tISCs at different time lags (5 lags of 2s in each direction). This approach revealed a peak correlation between the intact English and French tISCs at a 6s time lag. We adjusted for this shift by removing the first three time points of the English tISCs (to remove the lag) and the last three of the French tISCs (equalize lengths). Recomputing Pearson’s correlation with this shift revealed a significant correlation between the intact English and French tISCs, $r_{\text{English-French}}(24) =$
0.23, \( p = 0.005 \), as predicted by our third hypothesis (Figure 2e, f). No further correlations reached significance after adjusting for this time lag. The lag in the English audio occurs very early on (within the first 40s) and only contains an extended segment of music. Rather than affecting any of its intrinsic qualities, this lag simply delayed the unfolding of the narrative. Indeed, after accounting for the differences between the stimuli, we found a significant correlation between the intact English and French tISCs, which suggested that both versions captured similar neural processes related to plot-following.

However, it was not clear why a shift of 6s, rather than the full 10s, produced the maximal correlation. One possibility is that the resolution of the sliding window we used to compute the tISCs may have suppressed some of the early effects of the offset (Dehghani et al., 2019). Using a 5s sliding window with 3s of overlap, we calculated the tISCs at 2s time intervals throughout the audio. As such, the tISCs that occurred soon after the delay began likely contained some mixture of signals from before the delay and during, which may have washed-out its early effects. In fact, the cross-correlation analysis suggested that this was likely the case, as it revealed a sharp ramp-up of the correlation between the intact English and intact French tISCs just before the 6s shift and a gradual reduction just after. We reported only the correlation at the 6s shift because it most clearly illustrated the relationship between the English and French tISCs.
The number of time windows with significant tISCs during the intact English (21.71%; A) and the French audio condition (28.95%; B) were significantly more frequent than the scrambled conditions in either English (6.58%; C) or French (9.21%; D). Bottom panels show the overlap in time-shifted tISCs for the intact (E) and scrambled (F) English (blue) and French (red) audio conditions.

3.4 Discussion and conclusions

In this study, we developed a neural assessment protocol to index covert awareness in patients with severe brain injury using EEG and a naturalistic listening task. To accomplish this, we investigated whether ISCs in EEG activity could reliably index plot-following in healthy controls during French and English versions of “Taken”. The results presented here provide compelling support for this approach.

Overall, our findings were consistent with those reported in previous studies on movie-watching in fMRI (Naci et al., 2014, 2015) and EEG (Dmochowski et al., 2012; Ki et al., 2016). During movie-watching tasks, inter-subject neural synchronization reflects the
shared patterns of neural activity across people that are involved in processing both the sensory properties of the movie, as well as higher-order elements like its plot. As such, we expected to find significant inter-subject synchronization across our groups during each of the audio conditions. We also predicted that the added effect of the ‘coherent’ narrative would result in significantly higher overall ISCs for the intact conditions when compared to the scrambled conditions. While the ISCs for the intact English version of “Taken” were significantly higher than its scrambled counterpart, the ISCs for the French audio conditions were nearly identical. The most likely explanation for this difference lies in the ways the two language versions of the narrative were scrambled. The English audio was scrambled using spectral rotation, which retained many of the auditory properties of “Taken” but effectively removed any speech sounds from the clip. The scrambled version of the French audio was simply the intact version played backwards, which preserved all of its acoustic features but reversed the temporal structure of the plot. In this way, reversing the audio was a more ecological approach (Lerner et al., 2011), but this may have resulted in increased ISCs related to aspects of the preserved speech sounds. It is possible, for instance, that participants listening to the French version may have been able to glean some information about the overall nature of the plot from tonal changes in the voices (e.g., whispers, yelling), that were obscured in the spectrally rotated English scrambled version. In this case, participants may have synchronized to some degree through making similar predictions about the content of the narrative from its speech sounds or overall thematic qualities (e.g., its intensity, emotional valence). Still, the effects of the “Taken” audio on inter-subject synchronization in this study were clear across conditions. While the scrambling methods had a differential effect on the magnitude of ISCs between languages in our healthy group, this does not undermine the utility of this protocol in patients; both the English and French versions of “Taken” reliably produced comparable ISCs between groups which, as our later analyses suggested, captured similar processes related to plot-following (Naci et al., 2014, 2015).

The effect of the narrative, however, was much clearer when comparing the tISCs between the intact and scrambled versions of “Taken”. In both English and French, participants became synchronized significantly more often while listening to the intact,
rather than the scrambled audio. This finding highlighted the importance of accounting for the moment-to-moment fluctuations in synchronization as a narrative evolves over time. The tISCs also allowed us to directly compare the time course of synchronization between audio conditions and, importantly, to the suspense ratings for “Taken” acquired from an entirely different group of participants. Although we did not find any significant correlations between the tISCs across conditions, the tISCs for the intact English audio were significantly correlated with the suspense ratings, which provided additional evidence that the tISCs captured the neural activity specifically associated with following the plot of “Taken”. Likewise, the correlation between the suspense ratings and the tISCs for the intact French audio trended towards significance but unsurprisingly was not as strong as that of the correlation between English versions. Nevertheless, these combined results suggested that the higher-order processes involved in narrative processing like theory of mind, working memory, and attention (Ptak, 2012; Wolinski et al., 2018; Yeshurun et al., 2017) transcend linguistic contexts, which points towards a common mode of executive processing across languages (Naci et al., 2014, 2015). While some evidence of this been previously reported in fMRI (Honey et al., 2012; Yeshurun et al., 2017), to the best of our knowledge, our study is the first to demonstrate this effect using EEG.

The time-shifted correlations between the intact English and French tISCs warrant further discussion. We found a 10s difference between the two audio clips, which we predicted would have an effect on the temporal alignment of the ISCs between languages. This was indeed the case; when we compared the time course of the tISCs for the intact audio conditions, we found that they were not significantly correlated, despite capturing the same narrative over the same time scale and producing similar degrees and frequencies of inter-subject synchronization. Although this will not affect the implementation of this protocol in critical care centres, it was important to determine whether the tISCs for each language indexed similar neural processes. To explore this, we used a cross-correlation to compute the r-values at different time lags. This approach revealed a significant maximal correlation at a 6s shift in the English audio, which roughly corresponded to the offset of the narrative between clips. Although this technique was somewhat unorthodox, we
contend that if the tISCs between the intact English and French versions of “Taken” were completely unrelated, that is, if they did not capture the same neural processes associated with plot-following, the shift would not have affected the correlation between the two. However, this was not what we found; the shift in the English tISCs was precisely what we would have predicted given its 10s delay at the beginning of the clip and adjusting for this delay revealed a strong correlation between the tISCs in both languages for the intact audio. In a sense, this provided even stronger evidence that the CorrCA of the English and French versions of “Taken” captured similar neural processes because we found a strong relationship between the tISCs, despite the different linguistic properties of the stimuli as well as the asymmetrical timing of the clips. From these results, we can conclude that our EEG movie paradigm indexes similar aspects of plot-following and, therefore, conscious processing, in both English and French.

Our EEG assessment protocol has considerable potential as a novel brain-computer interface for detecting conscious processing in unresponsive individuals. Moreover, the testing procedures and analyses presented here could remain largely unchanged to assess awareness in patients in intensive care. First, rather than recalculate the CorrCA with the patient data, the existing component topography for the intact or scrambled version of “Taken” could be back-projected onto the patient EEG. This would effectively isolate the same pattern of activity and, in doing so, generate a new time course of component activity for each patient. As in healthy controls, this component time course could then be correlated with the healthy control group to produce the ISCs for individual patients, which could then be compared to a baseline of healthy control ISCs. The tISCs analysis, likewise, could be modified to determine when patients are significantly synchronized to the healthy group during “Taken”. This would involve iteratively calculating the ISCs between individual patients and healthy controls at each time point to generate a time course of tISCs. The time course of tISCs for patients could then be directly contrasted with the tISCs of a healthy control group or to the suspense ratings for “Taken”. Significant correlations between patients and controls, therefore, would suggest that they are processing the narrative of the clip in a way that is similar to healthy controls, which
could help inform future medical management and prognosis (Andrews et al., 1996; Childs et al., 1993).
References


Chapter 4

4 Identifying neural markers of naturalistic processing in patients with severe acute brain injury: A multi-method EEG approach

4.1 Introduction

Providing critical care for patients with severe acute brain injury is immensely challenging; rapid clinical assessments and intensive therapies are crucial during the initial hours and days after ICU admission, but uncertainties surrounding a patient’s mental state, as well as their likelihood of recovery, are numerous. However, while patient survival is paramount, prognostication of outcome plays a significant role in guiding the course of treatment. Factors like the type and severity of brain injury (e.g., traumatic, anoxic), behavioural responsiveness, and the length of time between injury and admission are all considered when planning how and, crucially, whether to continue treatment (Canabal Berlanga, 2020; González-Robledo et al., 2015; Joosse et al., 2009; Kulesza et al., 2015). Based on these metrics, poor prognosis may beget withdrawal of life-sustaining therapies (WLST) and the transition to end-of-life care (Connolly et al., 2016). A recent study found that of the 20% of all patients who die in the ICU, 60% resulted from withdrawing active treatment (Braganza et al., 2017). Therefore, it is critical that prognoses of survival and recovery—both of which inform the decision to withdraw life-sustaining measures—are made in an objective and unbiased manner with the best available tools and information.

However, significant variability exists between WLST practices across ICUs (Mark et al., 2015; Prendergast et al., 1998). A systematic review of WLST practices in adult ICU patients reported that the prevalence of patient mortality from WLST ranged from 0% to 84.1% across ICUs (Mark et al., 2015). What’s more, these practices varied substantially by region of the world, country, ICU, and even within an individual critical care center (Mark et al., 2015). Although legal differences in WLST practices globally, cultural traditions, and patient demographics could explain much of this variability (Barnato et al., 2012; Bosshard et al., 2008; Mark et al., 2015; Muni et al., 2011), physician opinion
and hospital-specific guidelines surrounding WLST play a significant role (Curtis & Barnato, 2014; Garland & Connors, 2007; Lee et al., 2020). Indeed, Garland and Connors (2007) reported that decisions to withdraw WLST were more strongly related to the identity of the attending physician than to patients’ acute diagnosis, presenting illness or injury, or comorbid conditions. Although these data are not specific to patients with serious brain injury, this trend raises significant concerns about the subjective nature in which prognosis (i.e., from standard clinical assessments) and decisions to WLST are made in critical care settings. One way to minimize prognostic variability—and variability in WLST practices generally—between health practitioners and ICU sites is to develop objective and quantifiable markers of brain function of patients in critical care.

Routine clinical assessments are a key part of standard of care for patients with serious brain injury. These frequently include structural imaging (e.g., computerized tomography [CT], MRI), neurological exams (e.g., cranial nerve function, reflexes), and behavioural measures of responsivity like the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1976). Although many of these assessments have been standardized and yield clinically meaningful information about a patient’s physical and mental state, their coarse, subjective, and largely behavioural nature limits their prognostic utility. As an example, somatosensory-evoked potentials (SSEPs)—an electrophysiological response to electrical stimulation of the median nerve—predict poor outcome in comatose patients with a high degree of accuracy; patients who do not produce SSEPs in response to nerve stimulation rarely show clinically meaningful improvements and their condition is likely to deteriorate over time. However, the presence of an SSEP response does not predict quality of outcome in coma—including those resulting from serious brain injury—survivors (Glimmerveen et al., 2020; Kane et al., 2017; Rossetti, 2017). Likewise, standardized neurological assessments like the GCS (Teasdale & Jennett, 1976) have many of the same limitations as the CRS-R (Kalmar & Giacino, 2005); both rely entirely on observable behaviour and involve subjective interpretations of, often subtle, responses (Coleman et al., 2009; 2009; Gibson et al., 2014; Owen, 2008, 2013). In this way,
functional neuroimaging could provide valuable insight into the neural and cognitive function of acutely comatose brain-injured patients, further informing outcome prediction to improve accuracy of prognosis (Duclos et al., 2020; Laforge, Incio Serra, et al., 2020).

Assessments of covert awareness and residual cognition that use functional neuroimaging have had an immense impact on the management and treatment of patients with chronic DOC (Kondziella et al., 2016; Owen, 2008, 2013). So immense, in fact, that the American Academy of Neurology recently updated its practice guidelines for patients with DOC to recommend functional neuroimaging in cases where behavioural evidence of awareness is lacking (Giacino et al., 2018). Given the success of neuroimaging in chronic DOC, it is likely that techniques like fMRI and EEG will provide deeper insight into the neurological factors that predict recovery of patients with acute DOC, in particular, acute coma. Acute coma is defined by a complete absence of wakefulness and awareness; comatose patients do not open their eyes and remain entirely behaviourally non-responsive (Laureys et al., 2009; Owen, 2008). Fortunately, coma is most often a temporary state lasting days or weeks. During this period, patients may die, recover partially or completely (though sometimes with Locked-in Syndrome), or transition into a chronic DOC such as a vegetative or minimally conscious state (Bernat, 2006; Laureys et al., 2004, 2005). Early detection of patients who will most likely survive or develop a chronic DOC would improve prognostic accuracy and, potentially, direct the course of treatment in ICU.

In recent years, the neuroscience of DOC has begun to focus on patients rendered comatose from acute severe brain injury. Indeed, taking cues from the chronic DOC literature, many studies have employed established techniques to assess acute DOC patients. These include investigations of resting-state BOLD and EEG activity to predict outcome (Pauli et al., 2020), neural examinations of sensory processing and speech detection (Chatelle et al., 2020; Sokoliuk et al., 2021), as well as covert command-following ability (Claassen et al., 2019; Edlow et al., 2017). Many studies have also incorporated machine learning algorithms into their outcome modelling to extract hidden features in BOLD or EEG activity that are associated with recovery (Chatelle et al., 2020; Claassen et al., 2019; Edlow et al., 2017).
During rest, preserved BOLD connectivity in the default mode network is predictive of better outcomes in patients with acute brain injury (Kondziella et al., 2017; Sair et al., 2018; Threlkeld et al., 2018). Additionally, quantitative analysis of relative EEG Alpha power and its variability improved prognostication of outcome in coma patients relative to standard clinical measures (O’Donnell et al., 2021). Multiple studies have also reported that early evidence of language processing and neural command-following (e.g., when patients are prompted to “Imagine moving your right hand”) are associated with better outcomes at 3 and 6 months (Chatelle et al., 2020; Claassen et al., 2019; Edlow et al., 2017; Sokoliuk et al., 2021).

While these findings support the use of functional neuroimaging to improve outcome prediction in acute coma, these approaches share many of the same limitations as in chronic DOC. For instance, fMRI is not an ideal imaging modality for DOC patients, as concerns regarding medical suitability and the risks incurred during transport to the fMRI suite are amplified in patients receiving critical care (Cruse et al., 2011; Laforge, Gonzalez-Lara, et al., 2020). Moreover, active task-based approaches, and those requiring multiple conditions and trials, may identify only the small number of patients who can respond consistently to task instructions and remain alert throughout long testing sessions. The “Taken” audio paradigm presented in Chapter 2 and 3, is less affected by these limitations and, for this reason, may serve as a novel tool to predict outcome after severe acute brain injury (Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020).

In this study, we administered the EEG “Taken” task to a small cohort ($N = 5$) of acutely comatose patients admitted to the ICU ($\leq 7$d) for severe traumatic or non-traumatic brain injury. Of note, unlike patients with chronic DOC, patients in acute coma often receive continuous pharmacological sedation to minimize pain and discomfort and stabilize vital physiological processes. Sedation is routinely paused, however, to perform neurological assessments and track recovery of function. As such, we presented the intact and scrambled versions of “Taken” to patients while they were on sedation and again after sedation was paused. In doing so, we aimed to determine whether early evidence of sensory and higher-order naturalistic processing, or the change in neural activity between
levels of sedation, have prognostic utility in patients with severe acute brain injury. We hypothesized that patients who recover would have retrospectively produced EEG markers of sensory and cognitive processes (e.g., plot-following) during the “Taken” task. Moreover, we hypothesized that changes in EEG activity between levels of sedation—indicative of a recovery of consciousness—would also be associated with outcome (Duclos et al., 2020). Specifically, we predicted that the magnitude of differences in ISCs and in whole-brain functional connectivity would be associated with recovery. Finally, we explored whether source-localized EEG activity from patients with better outcomes would be more comparable to the pattern observed in healthy controls during “Taken” than those with poor outcomes (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015).

4.2 Materials and methods

4.2.1 Patients and controls

Recruitment for this study took place between March 2020 and May 2021 at University Hospital and Victoria Hospital in London, Canada. Patients were deemed eligible for this study if they were over the age of 18, receiving treatment for severe primary (e.g., traumatic) or secondary (e.g., hypoxic) brain injury, admitted to ICU for 24hr-7d, and receiving continuous pharmacological sedation. Patients were excluded from this study if they had a history of open head injury, pre-existing cognitive impairments, or were otherwise considered medically unsuitable by critical care staff. In total, we enrolled six patients in this study (\(M\) age = 54.5, \(SD = 9.46\)) all of whom suffered hypoxic brain injury prior to ICU admission. All patients completed our EEG assessment protocol (Duclos et al., 2020), but one was excluded from further analysis due to excessive artifact contamination of their EEG (final \(N = 5\); see Table 2 for clinical demographic information). For the healthy control sample, we used the EEG data from the participants recruited for Chapter 2 (\(N = 15\)). Ethics approval for this study was granted by the Health Sciences Research Ethics Board and the Non-Medical Research Ethics Board of The University of Western Ontario (Appendix A).
Table 2. Clinical and Demographic Information for Patients with Severe Acute Brain Injury

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Assessment (years)</th>
<th>Sex</th>
<th>Interval post-injury</th>
<th>Etiology</th>
<th>GCS Score on Sedation (2T-15)</th>
<th>GCS Score off Sedation (2T-15)</th>
<th>Significant ISC on Sedation</th>
<th>Significant ISC off Sedation</th>
<th>Recovery (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>68</td>
<td>Female</td>
<td>3d</td>
<td>CA</td>
<td>3T</td>
<td>3T</td>
<td>--</td>
<td>--</td>
<td>Y</td>
</tr>
<tr>
<td>Patient 2</td>
<td>40</td>
<td>Female</td>
<td>2d</td>
<td>STEMI</td>
<td>3T</td>
<td>10T</td>
<td>--</td>
<td>Intact *</td>
<td>WLST</td>
</tr>
<tr>
<td>Patient 3</td>
<td>60</td>
<td>Female</td>
<td>2d</td>
<td>Stroke</td>
<td>6</td>
<td>6</td>
<td>--</td>
<td>--</td>
<td>N</td>
</tr>
<tr>
<td>Patient 4</td>
<td>58</td>
<td>Female</td>
<td>5d</td>
<td>CA</td>
<td>3T</td>
<td>3T</td>
<td>--</td>
<td>Intact *</td>
<td>Y</td>
</tr>
<tr>
<td>Patient 5</td>
<td>55</td>
<td>Male</td>
<td>3d</td>
<td>CA</td>
<td>3T</td>
<td>3T</td>
<td>--</td>
<td>--</td>
<td>Y</td>
</tr>
</tbody>
</table>

Note. CA, cardiac arrest – patients tested post resuscitation; STEMI, ST-elevated myocardial infarction; GCS, Glasgow Coma Scale; GSC score T, patient intubated. Intact *, denotes significant ISC with controls during the intact version of “Taken”, p < 0.05; WLST, withdrawal of life-sustaining treatment.

4.2.2 Procedures

Prior to testing, our research team coordinated with bedside staff to schedule our EEG assessment during planned withdrawals of pharmacological sedation. Per standard of care for acutely comatose patients, critical care staff periodically wean or withdraw sedation to perform neurological assessments like the Glasgow Coma Scale (GCS; Teasdale and Jennett, 1976). The GCS is a standardized measure used to categorize the severity of a suspected head injury and identify impairments in conscious awareness. It contains three subscales that score patients’ eye-opening, verbal, and motor responses to stimulation and verbal commands. GCS scores range from 2T (no responses across any of the subscales) to 15 (awake, aware, and fully responsive). Prior to withdrawal of sedation, our team prepared the testing equipment, applied the EEG sensor net, and ensured electrode impedances were below 50kΩ with minimal environmental noise contamination.

During the EEG assessment protocol, we presented the intact and scrambled clips from the English version of “Taken” to patients while they were receiving continuous pharmacological sedation and again after sedation was withdrawn (M = 33 min, SD = 11; Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020; Naci et al., 2015). A member of our research team instructed patients to listen carefully to each clip and to remain as still as possible until the end of the testing session. We presented the scrambled version of the audio before the intact version for all patients to remove any potential carryover effects of the narrative.
Stimulus presentation was controlled using the Psychtoolbox plugin for MATLAB (Kleiner et al., 2007) running on a 15” Apple MacBook Pro. The laptop screen remained blank (black) during the recording session. We played the “Taken” audio through a pair of Etymotics ER-1 in-ear headphones and adjusted the volume on a per-patient basis to account for any ambient noise levels. All EEG data were preprocessed and analyzed offline using MATLAB, EEGLAB (Delorme & Makeig, 2004), Brainstorm (Tadel et al., 2011).

4.2.3 EEG acquisition

EEG data were collected using a 129-electrode saline electrolyte cap (Electrical Geodesics Inc. [EGI], Oregon, USA) and the Netstation EEG acquisition software. During testing, the EEG signals were sampled at 250Hz and referenced online to electrode Cz. Our team ensured that electrode impedances were below 50kΩ before each condition (i.e., scrambled and intact, on and off sedation). Offline EEG cleaning followed standard preprocessing steps: we re-referenced the EEG to the common average, bandpass filtered the data between 0.5 – 60Hz (notch filter applied at 60Hz) and removed artifacts using a combination of automatic artifact detection and manual inspection. Severely noise-contaminated channels were removed from the data and replaced with a nearest-neighbour interpolation procedure. Finally, we performed ICA to remove artifact components and de-spiked the data to minimize the influence of non-systematic peaks in EEG amplitude on the analyses (Dmochowski et al., 2012). We performed all preprocessing steps separately for each stimulus condition, level of sedation, and patient.

4.2.4 Overview of analytic procedures

We performed three separate analyses on the “Taken” EEG data to explore the features of neural activity that may predict recovery of patients in an acute coma after serious brain injury. First, we performed a CorrCA (Cohen & Parra, 2016; Dmochowski et al., 2012; Ki et al., 2016; Laforge, Gonzalez-Lara, et al., 2020) to determine whether the patterns of neural activity exhibited by patients in the ICU during the intact and scrambled versions of “Taken” are statistically similar to those of healthy controls. As in the study described in Chapter 2, significant correlations in neural activity between patients and controls
suggest comparable processing of the stimuli and, importantly, comparable processing of its narrative. We predicted that significant correlations with controls during the task, or significant differences in ISCs between conditions (intact, scrambled) and level of sedation (on sedation, off sedation), would be associated with better recovery.

Second, we calculated inter-electrode magnitude-squared coherence to examine the functional connectivity profiles of healthy controls and ICU patients during “Taken”. Previous studies have shown that resting-state functional connectivity is associated with outcome in coma patients and, when combined with machine learning algorithms, outcome classification from connectivity data can outperform standard clinical prognostication (Carrasco-Gómez et al., 2021; Keijzer et al., 2021; Kustermann et al., 2019, 2020). However, to the best of our knowledge, no studies have investigated task-based EEG connectivity during the acute stages of severe brain injury. We predicted that functional connectivity during the “Taken” task—which was specifically designed to engage multiple sensory and cognitive systems—would be associated with survival and later cognitive outcome (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2014, 2015).

Finally, we performed a simplified version of the EEG source localization procedure presented in Chapter 2 to determine whether differential cortical activations during the “Taken” audio (e.g., areas of the fronto-parietal network) were associated with recovery. Our goal with these analyses was to identify patterns of neural activity across multiple levels of analysis—or changes therein between conditions (intact, scrambled) and level of sedation (on sedation, off sedation)—that may improve prognostic accuracy in acutely comatose patients.

4.2.5 Correlated components analysis

As in Chapter 2 and 3 we performed a CorrCA to calculate ISCs between ICU patients and healthy controls during the intact and scrambled versions of “Taken” (Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020). Briefly, the CorrCA identifies linear combinations of EEG activity that are maximally correlated between all subjects in the data (Cohen & Parra, 2016; Dmochowski et al., 2012; Ki et al., 2016). Like other types of components analysis, CorrCA generates a set of voltage topographies
(components) and time courses that are rank-ordered by the magnitude of their correlation. As in Study 1 and Study 2, we focused our analyses on the top-ranked EEG components from the intact and scrambled versions of “Taken”, as they reflect the neural activity associated with processing the auditory features of the clip as well as its plot (Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020).

To calculate ISCs, we identified the top-ranked component across the group and back-projected its spatial weights onto the EEG data from each subject to isolate its time course. We then correlated the time courses between all pairs of participants and computed the average correlation coefficient between each participant and the rest of the group. The average correlation for each participant represented their individual ISCs. Finally, we used a leave-one-out approach combined with permutation testing to establish a threshold for statistical significance for each subject. Specifically, we iteratively recalculated the CorrCA, leaving one participant out during each iteration, and used the subsequent component topography and time course to calculate unbiased ISCs for each (left out) participant. To determine the statistical significance of the ISCs, we phase-shifted the time course of correlation coefficients between participants and performed a 1000 iteration resampling procedure to generate null distributions of correlation coefficients for each subject. Mean ISCs with a magnitude that exceeded the top 5% of the null distribution were interpreted as statistically significant. To compute the ISCs between patients and controls, we back-projected the spatial weights of the top-ranked component from the healthy control groups onto the EEG data from individual patients. This produced a time course of component activity for each patient to correlate with that of the healthy control group. The absolute correlation coefficient for each patient represented the similarity of their neural activity to healthy controls during “Taken”. We then tested the statistical significance of the absolute correlation coefficient for each patient, audio condition, and level of sedation using the same permutation approach used in the control group.
4.2.6 Inter-electrode coherence

We have shown that the CorrCA can be used to assess sensory and cognitive processing in behaviourally non-responsive patients (Laforge, Gonzalez-Lara, et al., 2020). However, this approach only incorporates one dimension of the EEG data into its calculations, namely, the fluctuations in EEG amplitude over time. The CorrCA does not, for instance, account for changes across other features of the EEG signal like its frequency or phase (Dmochowski et al., 2012; Ki et al., 2016). As such, CorrCA is not, strictly speaking, a measure of functional connectivity; rather, it combines discrete patterns of EEG activity to maximize correlations at the group level. More traditional measures of EEG functional connectivity often integrate multiple dimensions of the EEG signal to establish functional relationships in cortical neuronal activity (Bastos & Schoffelen, 2016; Olejarczyk et al., 2017; Sakkalis, 2011; Sarmukadam et al., 2020). This additional depth of analysis may further inform clinical prognostication of outcome in acutely comatose patients. To this end, we calculated inter-electrode magnitude-squared coherence—a commonly used measure of functional connectivity—to explore the frequency dynamics of EEG data collected from individual patients in the ICU during “Taken” (Keijzer et al., 2021; Kustermann et al., 2019, 2020; Lehembre et al., 2012).

Magnitude-squared coherence (MATLAB function ‘mscohere’) is an analysis technique frequently applied to EEG data to quantify the phase synchrony between brain areas (Bastos & Schoffelen, 2016; Bowyer, 2016). Coherence is mathematically similar to a cross-correlation in that its squared value captures the amount of variance in one EEG signal that can be explained by another. However, magnitude-squared coherence operates along the frequency domain rather than time (Bastos & Schoffelen, 2016). Magnitude-squared coherence estimates the shared variance between signals \( x \) and \( y \) in each frequency as a function of the power spectral densities \( P_{xx} \) and \( P_{yy} \) and the cross-power spectral density \( P_{xy}(f) \):
This procedure yields an estimate of the functional connectivity between $x$ and $y$ from 0 (no phase synchrony) to 1 (perfect phase synchrony) within a given frequency range and resolution. Magnitude-squared coherence can also be calculated using a temporal sliding window technique, similar to the tISCs described in Studies 1 and 2, to track dynamics in EEG phase synchrony over time (Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020).

For this analysis, we calculated inter-electrode magnitude-squared coherence on the EEG data collected from individual healthy participants from Study 1 and ICU patients during the “Taken” task. We computed the coherence between all possible pairs of EEG electrodes in 1s time bins from 0.5 - 55Hz with a frequency resolution of 0.25Hz. We then averaged the coherence coefficients for each channel pair for each subject and binned them into the canonical EEG frequency bands (Delta 0.5 - 4Hz, Theta 4 - 8Hz, Alpha 8 - 12Hz, Beta 13 - 30Hz, Gamma 30 - 55Hz). Finally, we calculated the mean coherence within each frequency band for each subject averaged over time. This produced a single coherence coefficient within each frequency band, representing the average whole-brain coherence across the total duration of “Taken”.

In order to meaningfully assess EEG coherence in acutely brain injured patients, we first needed to establish a baseline of coherence in healthy controls during the “Taken” task. We calculated inter-electrode coherence among the control sample and performed a 2 x 5 repeated measures ANOVA with audio condition and frequency band as factors. This enabled us to quantify the overall EEG coherence among the healthy participants, explore how coherence is distributed across different EEG frequency bands, and determine whether either differed between audio conditions. We repeated this analysis on the coherence data from ICU patients while they were on and off sedation to identify any systematic differences in coherence relative to controls. To compare coherence between patients and controls directly, we also performed a 2 x 5 x 2 mixed design ANOVA, both while patients were on and off pharmacological sedation, with audio condition, frequency, and group as factors,
We also explored how patients’ neural activity changed in response to the different audio conditions across different levels of sedation, and whether the extent of these changes was associated with survival and recovery (Duclos et al., 2020). To this end, we performed a 2 x 5 x 2 mixed design ANOVA to compare the magnitude of the difference in coherence between each level of sedation across audio conditions (e.g., intact audio on sedation minus intact audio off sedation). This model included audio condition and EEG frequency as repeated measures factors and survival as a binary between subjects factor. We then performed a follow-up 2 x 5 x 2 mixed design ANOVA to compare the magnitude of the difference in coherence between audio conditions across levels of sedation (e.g., intact audio on sedation minus scrambled audio on sedation). For this model, we included level of sedation and EEG frequency as repeated measures factors and survival as a binary between subjects factor.

4.2.7 Cortical source reconstruction

Finally, we performed a source localization procedure on the EEG data from the patient sample to determine whether differences in cortical activation between audio conditions or between levels of sedation were associated with recovery. For this analysis, we performed a simplified version of the source reconstruction technique described in Study 1 (Laforge, Gonzalez-Lara, et al., 2020). We used the Brainstorm plugin for MATLAB and its built-in OpenMEEG software to generate head and cortical models for each patient based on MNI templates (Gramfort et al., 2010; Tadel et al., 2011). We chose to use the standard model templates rather than those constructed from individual T1-weighted structural MRI scans, as in Study 1, due to the limited availability of MRI scans in this sample. The standard head model (called a forward model) specifies the conductive properties of the skin, skull, white matter, grey matter, and cerebrospinal fluid to estimate the cortical electrical currents from the electrical potentials recorded by the EEG sensors (Gramfort et al., 2010). With the forward model, the Brainstorm software applies an inverse model solution to localize the likely source of the activity on 3D cortical surface model made from a folded tessellated flat map of 2D voxels or “vertices” (Gramfort et al., 2010; Tadel et al., 2011). All cortical surface models used in this study contained 15,002 vertices to balance spatial resolution with computational cost.
Like Study 1, we applied a wMNE inverse model to identify the cortical generators of the EEG activity recorded from patients during “Taken” (Laforge, Gonzalez-Lara, et al., 2020). The wMNE approach treats source reconstruction of EEG data as a linear imaging problem such that the current density at the level of the cortex approximates the observed EEG data when filtered through the forward model. wMNEs apply a regularization constraint (in this case, Tikhonov regularization) to favour minimum energy solutions that more closely approximate biologically plausible electrical currents. This method also controls for systematic noise in the data by modelling the noise at baseline (i.e., before the “Taken” audio begins) to improve solution accuracy. Finally, wMNEs apply a depth-weighting to the inverse solutions to amplify sources that are deeper in the cortex (e.g., within sulci) that may otherwise be overwhelmed by more superficial sources (Gorodnitsky et al., 1992; Hämäläinen, 2010; Hincapié et al., 2016). Like regularization and noise modelling, depth-weighting improves the accuracy and biological plausibility of the source solutions.

In general, wMNEs apply a linear inverse operator to the EEG data observed over \(N\) channels. With an \(M \times N\) matrix, where \(M\) is the number of sources, the linear inverse operator follows a Bayesian approach

\[
M = R'G^T(GR'G^T + C)^{-1}
\]

where \(G\) is the gain matrix of the strength of the sources, \(C\) is the noise covariance matrix, and \(R'\) is the covariance of the sources. Current amplitudes at time \(t\) are calculated as

\[
\hat{j}(t) = M_x(t)
\]

where \(x(t)\) is the EEG at time \(t\). To regularize the source estimates, the unknown variance of the current is expressed as \(R' = R/\lambda^2\) which produces the inverse operator

\[
M = RG^T(GRG^T + \lambda^2C)^{-1}
\]
where the amplitude of the unknown current is estimated as the regularization parameter $\lambda^2$. wMNEs also minimize the cost function of the solutions as

$$S = \hat{e}^T \hat{e} + \lambda^2 j^T R^{-1} j$$

where the first term represents the difference between whitened EEG data and the activity predicted by the model and the second term is the weighted norm of the current estimate. As $\lambda^2$ increases, the source term receives additional weight and larger differences between the predicted and real data become more acceptable (Hämäläinen, 2010). After data whitening and scaling, the noise covariance matrix $C$ is regularized as

$$C'' = C + \sum_k \varepsilon_k \sigma_k^{-2} I^k$$

where $k$ moves across the EEG channels (with regularization factors $\varepsilon_k$, $\sigma_k^{-2}$ which represent the average variances across channels) and $I^k$ are diagonal matrices of ones for the channels in each group. After regularization of the covariance matrix, the source solutions can be solved for using an expression of the inverse operator. These predicted solutions are then noise-normalized and compared to the measured data to quantify the correctness of the regularization procedure. Finally, source estimates are adjusted to conform to the anatomical constraints of the cortices and weighted for depth (Hämäläinen, 2010).

We applied a wMNE solution to the EEG data collected from patients during the intact and scrambled versions of “Taken” both while they were on and off pharmacological sedation. Unlike the source reconstruction procedure described in Study 1, we did not regress the CorrCA component time course onto patient cortical activity. Instead, we examined the initial source solutions to determine whether differences in overall cortical activation—not just those corresponding to a single component—were associated with recovery from severe brain injury. To this end, we computed the wMNE at each time point in the EEG recordings (250Hz over 5 min.) for each patient, condition, and level of sedation.

Here, we performed paired one-directional Wilcoxon sign-rank tests to identify significant differences in source activity between the intact and scrambled audio
conditions at each level of sedation (intact > scrambled; scrambled > intact; on and off sedation). We predicted that, if the “Taken” paradigm is effective in acutely comatose patients, we would find differential activation of the fronto-parietal and temporal cortices during the intact and scrambled audio conditions. We also expected that differences in cortical activation during each condition would be reduced while patients were on sedation; however, the combined effects of acute brain injury and pharmacological sedation on narrative processing are not well understood (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015). We then contrasted the source estimates within the same audio condition when patients were on and off sedation (intact audio off sedation > intact audio on sedation) using the same statistical procedure. Finally, we performed an independent Student’s t-test to identify differences in the source activity between the group of patients who survived (N = 3) and those who did not (N = 2) to detect potential neural markers of survival. Statistical significance for all tests was established using a 100,000 iteration Monte Carlo simulation procedure.

4.3 Results

4.3.1 Inter-subject synchronization in acute brain injury

We analyzed the EEG data from the patient sample using a CorrCA to investigate whether their neural activity was suggestive of higher-order cognitive processing during “Taken”. First, we calculated the CorrCA for each patient during the scrambled version of “Taken”. At the group level, the absolute ISCs for 3/5 (60%) of patients decreased after sedation was withdrawn, though this was not statistically significant across the group, t(4) = 0.984, p = 0.809. None of the five patients in this sample showed significant ISCs with the control group during the scrambled audio condition (Figure 6A). This was the case while patients were receiving pharmacological sedation (M = 0.014, SD = 0.010) and after sedation was withdrawn (M = 0.009, SD = 0.003). During the intact version of “Taken”, the absolute ISCs for 4/5 patients increased significantly after pausing sedation, t(4) = 2.280, p = 0.042. While on sedation, none of the patients were significantly correlated to the controls (M = 0.012, SD = 0.009). However, after sedation was
withdrawn ($M = 0.020, SD = 0.012$), Patient 2 and Patient 4 (2/5; or 40%) showed significant ISCs with controls (Figure 6B).

We predicted that significant correlations with controls during the intact version of “Taken” would predict survival and, potentially, overall degree of recovery. However, Patient 4 was the only patient who both survived and was significantly correlated to controls during this task; Patient 2 was also significantly correlated with the healthy group but life-sustaining treatment was eventually withdrawn due to poor clinical prognosis related to complications from pneumonia. Conversely, Patient 1 and Patient 5 also survived but did not show significant ISCs with controls during the task. Overall, these results provide mixed evidence for the utility of the CorrCA during the “Taken” task to predict outcome in patients with acute severe brain injury.

Figure 6. Magnitude of ISCs between patients with acute brain injury and healthy controls.

A) The magnitude of the ISCs between healthy controls and individual patients during the scrambled version of “Taken” while patients were receiving pharmacological sedation (panel A left) and after sedation was paused (panel A right). B) The magnitude of the ISCs between healthy controls and individual patients during the intact version of “Taken” while patients were receiving pharmacological sedation (panel B left) and after sedation was paused (panel B right). Note: * signifies statistically significant ISCs ($p < 0.05$).
4.3.2 Coherence dynamics during naturalistic auditory stimulation

In addition to the CorrCA, we analyzed functional connectivity in patients and controls during the “Taken” paradigm. To establish a baseline of coherence during the “Taken” task, we calculate inter-electrode coherence among the healthy control group from Study 1. A 2 x 5 repeated measures ANOVA revealed that mean inter-electrode coherence was not significantly different between audio conditions, $F(1,14) = 3.225, p = 0.094$.

However, coherence was not uniformly distributed across frequency bands, $F(4, 56) = 34.40, p < 0.001, \eta^2_p = 0.711$; mean coherence in the Delta frequency band (0.5 – 4Hz) was significantly higher than Theta (4 – 8Hz), Beta (12 – 30Hz), and Gamma (30 – 55Hz). Additionally, coherence in Theta and Alpha were significantly higher than both the Beta and Gamma frequencies (Figure 7) across conditions (Tukey HSD $p < 0.05$, Holm corrected). There was no significant interaction between condition and frequency, $F(4, 56) = 0.396, p = 0.811$. These results showed that inter-electrode coherence during “Taken” was most prominent among lower frequencies and decreased systematically across higher frequency bands.

We repeated this analysis to explore whole-brain functional connectivity in patients across audio conditions and different levels of sedation. First, we performed a 2 x 5 repeated measure ANOVA on the intact and scrambled audio conditions within the same level of sedation (e.g., scrambled audio vs intact audio on sedation). However, we did not find any significant differences in inter-electrode coherence across condition, $F(1, 4) = 0.121, p = 0.746$, frequency band, $F(4, 16) = 2.731, p = 0.066$, or any interaction between the two while patients were on sedation, $F(4, 16) = 0.467, p = 0.759$, (Figure 8A).

Similarly, we did not find any significant differences in coherence between audio conditions, $F(1, 4) = 0.958, p = 0.383$, or frequencies, $F(4, 16) = 1.673, p = 0.205$, and no interaction, $F(4, 16) = 1.887, p = 0.162$, after sedation was withdrawn (Figure 8B).
Mean coherence across all EEG channels among healthy controls during the scrambled (left) and intact versions of the “Taken” audio. Although there was no systematic difference in coherence between audio conditions, coherence varied significantly between frequency bands, irrespective of audio condition. Note: error bars reflect standard error.

Our next analyses focused on the mean coherence within each audio condition between levels of sedation (e.g., scrambled audio on sedation vs. scrambled audio off). For the scrambled audio condition, we found no significant differences in coherence between level of sedation, $F(1, 4) = 0.343$, $p = 0.590$, or frequency band, $F(4, 16) = 1.328$, $p = 0.302$, nor did we find a significant interaction between these factors, $F(4, 16) = 0.508$, $p = 0.731$ (Figure 8A). However, a 2 x 5 repeated measures ANOVA revealed a significant effect of frequency, $F(4, 16) = 3.794$, $p = 0.024$, $\eta^2_p = 0.487$, during the intact audio condition, though only between the Delta (0.5 – 4Hz) and Alpha (8 – 12Hz) bands (Tukey HSD $p = 0.031$, Holm corrected).
Figure 8. Inter-electrode coherence between patients with acute brain injury during the “Taken” task.

A) Mean inter-electrode coherence across patients during the scrambled (panel A left) and intact (panel A right) versions of “Taken” while receiving continuous pharmacological sedation. B) Mean inter-electrode coherence across patients during the scrambled (panel B left) and intact (panel B right) versions of “Taken” after sedation was paused. As in healthy controls, there were no significant difference in EEG coherence between audio conditions at either level of sedation. Additionally, there were no systematic differences in mean inter-electrode coherence between EEG frequency bands. Note: error bars represent standard error.

We then compared the functional connectivity across patients to the healthy control group to identify any group-level differences in coherence during the “Taken” task. We accomplished this by performing a 2 x 5 x 2 mixed-design ANOVA on the coherence data from the control group and patients while they were on and off sedation. While patients were on sedation, we found a significant effect of frequency across both groups, $F(4, 72) = 15.55, p < 0.001, \eta^2_p = 0.464$, and a significant frequency by group interaction, $F(4, 72) = 4.599, p = 0.002, \eta^2_p = 0.204$. On the frequency factor, mean coherence was highest in the Delta frequency band for all participants and patients (Tukey HSD $p < 0.001$, Holm corrected). For the frequency by group interaction, coherence was highest
among the lower frequency bands for healthy controls. We found a similar effect in patients, as Delta coherence was significantly higher than in the Alpha band (Tukey HSD $p < 0.001$, Holm corrected).

When patients were off sedation, we found a similar main effect of frequency, $F(4, 72) = 11.091, p < 0.001, \eta^2_p = 0.381$, and another frequency by group interaction, $F(4, 72) = 4.752 p = 0.002, \eta^2 = 0.209$. Like the previous analysis, mean coherence in Delta was significantly higher than in any other frequency band across all participants (Tukey HSD $p \leq 0.001$). However, the frequency by group interaction was slightly different; here, we found that Delta coherence among healthy controls was significantly higher than Beta or Gamma. Coherence in the Theta and Alpha frequencies was significantly higher than in Gamma for the control group. Lastly, the magnitude of Delta coherence in patients was significantly higher than Gamma coherence in the control group (Tukey HSD, $p < 0.001$ Holm corrected). Overall, these analyses found only minor differences in mean coherence between patients and controls, though significant differences exist between EEG frequencies across all participants.

Although we did not find any significant differences in coherence within the patient group, we further explored these data by analyzing the absolute differences in mean coherence between audio conditions (i.e., scrambled minus intact) and levels of sedation (i.e., on sedation minus off sedation). We performed two separate 2 x 5 x 2 mixed design ANOVAs to determine whether differences in coherence across frequency bands, either between levels of sedation or audio conditions, were associated with patient survival. First, we computed the absolute difference in coherence between levels of sedation within each frequency band and compared the magnitude of these differences between audio conditions. In this analysis, two significant interactions emerged. First, we found a significant condition by frequency interaction, $F(4, 12) = 10.122, p < 0.001, \eta^2_p = 0.771$. However, given the low statistical power of this sample, none of the post hoc contrasts survived correction for multiple comparisons. We also found a significant three-way interaction between frequency, condition, and survival, $F(4, 12) = 5.875, p = 0.007, \eta^2_p = 0.662$ but, like the previous interaction effect, no follow-up contrasts survived correction for multiple comparisons (Figure 9A).
Finally, we examined the absolute difference between audio conditions at each level of sedation to determine whether mean coherence was associated with survival after severe brain injury. We found a significant three-way interaction between level of sedation, frequency, and survival, $F(4, 12) = 4.907, p = 0.014, \eta^2_p = 0.621$. While none of the post hoc comparisons remained significant after correction, we performed a repeated contrast analysis on the interaction term. This analysis revealed that differences between audio conditions in the Beta (13 - 30 Hz) and Gamma (30 - 55 Hz) frequencies across levels of sedation may be associated with survival.

Figure 9. Differences in EEG coherence among patients between levels of sedation and audio condition.

A) The absolute difference in inter-electrode coherence during “Taken” between levels of sedation (on sedation – off sedation) for patients who did not recover from their injury. B) The absolute difference in inter-electrode coherence during “Taken” between levels of sedation for patients who recovered. Although this analysis revealed two significant interactions, neither survived correction for multiple comparisons. C) The absolute
difference in inter-electrode coherence between audio conditions (scrambled – intact) across levels of sedation for patients who did not recover from their injury. D) The absolute difference in inter-electrode coherence between audio conditions across levels of sedation for patients who recovered. There was a significant three-way interaction between level of sedation, frequency, and survival. Repeated contrasts revealed that differences in Beta and Gamma coherence could differentiate the two patient groups \( p < 0.05 \).

Surprisingly, this analysis revealed that differences between audio conditions in the Beta (compared to Gamma) and Gamma frequencies \( p < 0.05 \) were higher for patients who did not recover. In other words, patients who would not survive their injury showed increased variability among higher frequencies during the “Taken” task than those who would (Figure 9B). This suggests that the stability of functional connectivity between levels of sedation may be clinically informative and could be used to improve prognostication after serious brain injury (Duclos et al., 2020, 2021).

4.3.3 Cortical reconstruction of EEG activity across conscious states

For the final analysis of this study, we conducted a source localization analysis on the EEG activity from ICU patients during “Taken” to identify cortical activity that may predict survival and later recovery from severe brain injury. We applied a wMNE to the full (5 min.) EEG recordings from each patient and performed group-level contrasts on the localized cortical activity across audio conditions and level of sedation. We predicted that disparities in cortical activations during “Taken” may provide additional prognostic information and could be used in conjunction with the CorrCA and inter-electrode coherence techniques to inform prognosis. All statistical tests were performed in a vertex-wise fashion between conditions or group and was established using a permutation test approach. Cortical regions were identified using Brainstorm’s Desikan-Killiany atlas (Tadel et al., 2011).

We first examined the differences in cortical activation between the intact and scrambled versions of “Taken” while patients were on sedation. We performed two one-directional
paired Wilcoxon signed-rank tests on the activations from all patients, irrespective of outcome. During the intact audio condition (intact > scrambled), we found significantly higher activation in bilateral superior parietal cortex and in the right anterior region of the mid-frontal lobe (Figure 10A). During the scrambled audio condition (scrambled > intact), we found significantly higher activation across the left temporal lobe down to the temporal pole, as well as small areas of activity in the right inferior frontal gyrus and lateral left post-central gyrus (Figure 10B).

We used the same statistical procedure to contrast patients’ cortical activity during the intact and audio scrambled conditions after pharmacological sedation was withdrawn. For the intact version of “Taken” (intact > scrambled), we found significantly higher bilateral activations in anterior regions of the mid-frontal cortex, the left superior and inferior frontal gyri, areas of the left postcentral gyrus, and the right inferior temporal cortex (Figure 11A). In contrast, during the scrambled version of “Taken” (scrambled > intact), our analyses revealed higher activations in the orbitofrontal and pre-central gyri, as well as in the inferior, mid-, and superior temporal cortices (Figure 11B). Interestingly, the differences in cortical activation between the two audio conditions were comparable to those found among healthy controls in Study 1 and in fMRI, irrespective of level of sedation (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015). While the differences in cortical activity between audio conditions were less pronounced in acutely comatose patients, the differential activations across fronto-parietal and temporal cortices suggest that the “Taken” paradigm remains effective in patients with acute DOC.
Figure 10. Comparisons of source reconstructed EEG from patients receiving continuous pharmacological sedation during the “Taken” task.

A) Areas where source reconstructed EEG activity was significantly higher during the intact version of “Taken” while patients were on sedation. B) Areas where source reconstructed EEG activity was significantly higher during the scrambled version of “Taken” while patients were on sedation. Note: red areas represent significant t values ($p < 0.05$ after Monte Carlo simulation).

To determine whether source localized neural activity has prognostic clinical utility, we performed independent permutation $t$-tests to compare cortical activity during the “Taken” task between patients who survived and those who did not. While patients were on sedation, we found only sparse islands of activity (i.e., single vertex differences) that differentiated the groups in either audio condition, which most likely reflected noise or
Figure 11. Comparisons of source reconstructed EEG from non-sedated patients during the “Taken” task.

A) Areas where source reconstructed EEG activity was significantly higher during the intact version of “Taken”. B) Areas where source reconstructed EEG activity was significantly higher during the scrambled version of “Taken”. Note: red areas represent significant t values (p < 0.05 after Monte Carlo simulation).

statistical error. The same was largely true for patients while they were off sedation as well, with the exception of one small patch of activity in the mid-frontal cortex that was significantly higher for survivors during the intact version of “Taken”. Although the magnitude of the difference in this area was relatively high compared to the previous contrasts it too was most likely a statistical artifact because of its limited spatial extent (Hassan et al., 2014). Overall, the results of the source localization analyses were somewhat aligned with our predictions about the utility of the “Taken” task in acutely comatose patients. However, given the small sample size in this study, establishing, and verifying its prognostic value will require further research.
4.4 Discussion

4.4.1 Main findings

The primary aim of this study was to determine whether the “Taken” paradigm could be used to identify EEG markers of preserved sensory and cognitive function in patients with severe acute brain injury. Here, we developed two general hypotheses: 1) patients who recover are more likely to have produced neural activity indicative of sensory and cognitive processing during the “Taken” task and 2) the magnitude of the changes in EEG activity between levels of sedation would be associated with outcome (Duclos et al., 2020; Laforge, Gonzalez-Lara, et al., 2020; Laforge, Incio Serra, et al., 2020). Overall, we can draw three main conclusions from this study.

First, we found that two of five patients could produce patterns of neural activity comparable to healthy controls during the “Taken” task. The EEG activity from Patient 2 and Patient 4 was significantly correlated with healthy controls’ (significant ISCs) during the intact version of the audio but only while they were off sedation. Second, we found marginal evidence that differences in EEG functional connectivity between audio conditions may be related to outcome; differences in high-frequency inter-electrode coherence were significantly smaller for patients who recovered from their injury. Importantly, this pattern of connectivity was similar to what we observed among healthy controls, specifically, that connectivity did not differ significantly between audio conditions in the control group. While this suggests that stability among high-frequency brain networks could be an indicator of good recovery, given the small sample size of the patient group, this finding should be interpreted with caution. Finally, we observed that the patterns of source localized EEG activity among ICU patients listening to “Taken” were somewhat aligned with previous findings in healthy controls (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015). EEG activity primarily arose from frontal and parietal cortices during the intact audio condition, whereas the scrambled audio generated more activity from temporal regions. Although cortical activity alone could not differentiate patients with good and poor outcomes, these findings support the use of the “Taken” paradigm in this population.
4.4.2 Patient outcomes: Sensitivity, specificity, and practical considerations

Patient mortality was the main outcome measure used in this study. Three of the five patients who underwent EEG assessment recovered: Patient 1, Patient 4, and Patient 5. Of these patients, only Patient 4 showed significant ISCs with healthy controls during the intact version of “Taken”. Although a test sensitivity of 33% is relatively low, there are many factors to consider when interpreting this result. Principally, the heterogeneity between patients with acute serious brain injury poses a significant challenge, especially in limited samples like the one presented here. Variables like injury type and severity, or the time between hospitalization and EEG assessment make it difficult to validate novel prognostic tools, especially in limited samples. Another significant consideration is the brief window of time in which our assessments occurred. Like patients with chronic DOC, patients with acute brain injury experience fluctuations in wakefulness and awareness, which decreases the likelihood of capturing a patient’s true cognitive state in a single assessment (Bareham et al., 2018, 2020). Similarly, patients may be experiencing delirium—a common symptom of serious brain injury—which, even if patients were awake and aware, would have inhibited their ability to follow the narrative (Ganau et al., 2018; Maneewong et al., 2017). In this way, performing neural assessments at multiple time points throughout a patient’s stay in hospital would increase the probability of detecting significant ISCs during “Taken” (Laforge, Gonzalez-Lara, et al., 2020).

In a similar vein, we designed our assessment protocol around routine withdrawals of sedation. This enabled us to examine the degree to which patients’ neural activity reconfigured when they regained wakefulness and, perhaps, awareness. However, this approach also introduced additional confounds to the study. Principally, all patients in this study received pharmacological sedation before EEG testing. Previous research has shown that anesthetic agents have a profound and lasting impact on neural activity (Chen et al., 2009; Colon et al., 2017; MacDonald et al., 2015) which may have biased our comparisons to EEG data from non-sedated healthy controls. Likewise, the type of sedative(s) administered, the amounts given, and individual metabolic rates affect the depth of sedation and its duration, further complicating our interpretation of these results.
(Hans et al., 2005; Park et al., 2020; Waschkies et al., 2015). Although we worked closely with critical care staff to ensure patients’ physiological status indicated a return to baseline after sedation was withdrawn, we cannot discount the possibility that its residual effects influenced these results.

The significant ISCs exhibited by Patient 2 during the “Taken” task also warrants further interpretation. Both Patient 2 and Patient 4 showed significant ISCs with healthy controls during the intact version of the audio. Unfortunately, unlike Patient 4, Patient 2 did not recover from her injuries. While this reduced the overall specificity of our paradigm (50% true negative; 50% false positive), it is worth noting that Patient 2 was highly reactive after sedation was withdrawn. So reactive, in fact, that she remained on continuous sedation, in part, to reduce her agitation and ensure that her behaviour did not pose a risk to her treatment. By all accounts, Patient 2 was awake and at least minimally aware of her surroundings during the second presentation of “Taken” and her significant ISCs with controls likely reflected this. Additionally, Patient 2 did not succumb to her primary injury, but from complications related to pneumonia. As such, we cannot know whether Patient 2 would have survived her brain injury. Nevertheless, her behaviourally responsivity and significant ISCs suggested that she retained the cognitive capabilities to process the audio which, in other contexts, have been shown to predict better outcome (Chatelle et al., 2020; Claassen et al., 2019; Sokoliuk et al., 2021).

Comparing the functional connectivity among the patients in this sample, we found two EEG features that distinguish survivors from non-survivors. Namely, the magnitude of the difference in EEG coherence between audio conditions (i.e., between intact and scrambled “Taken”) was higher in the Beta and Gamma frequencies for patients who did not survive. This finding is somewhat unique with respect to previous studies that, for the most part, report that EEG activity among lower frequencies (i.e., Delta – Alpha) are most associated with recovery (O’Donnell et al., 2021; Pauli et al., 2020). However, many of these studies focused on resting state EEG and none have used naturalistic narrative stimuli. Naturalistic stimuli like movies and stories differentially modulate EEG activity across a broad frequency spectrum. Indeed, Alpha activity is often associated with attentional processes during naturalistic perception (Dmochowski et al., 2012; Ki et
al., 2016), Beta oscillations have been shown to predict individual movie preferences and are involved in reward processing (Boksem & Smidts, 2015; Christoфорou et al., 2017), and the Gamma band has been linked to theory of mind and emotion (Panzica et al., 2019; Yang et al., 2020). During naturalistic tasks, therefore, we might expect broadband differences in EEG activity across task conditions, levels of awareness, and, here, injury severity or comorbid pathologies.

Although it is beyond the scope of this study to uncover the cognitive or physiological bases of the differences we found between Beta and Gamma connectivity in this sample, it is important to highlight the similarity in EEG connectivity between healthy controls and survivors. Neither healthy controls nor patients who survived their injury showed significant differences in EEG coherence between the two audio conditions. This was not the case for non-survivors; non-survivors showed larger differences in Beta and Gamma coherence during the intact audio condition. While the clinical implications of this effect are unknown, variability in Beta and Gamma coherence during the “Taken” task may provide an early brain-based marker of recovery in this population. However, additional research is needed to replicate this effect and determine if it is statistically reliable among larger cohorts of patients with severe acute brain injury.

4.4.3 True coma and secondary brain injury

Compared to other DOC, the comatose state is arguably the most severe. Patients in a coma do not exhibit behavioural or neurological signs of wakefulness, nor do they produce behavioural responses to stimulation or their environment (though reflex movements may be preserved). Fortunately, true coma is rare and often resolves quickly (Laureys et al., 2004, 2009; Tart, 2001; Teasdale & Jennett, 1976; Young, 2000). During this period, however, patients in ICU often receive continuous pharmacological sedation to stabilize and regulate vital processes and minimize their discomfort. In effect, standard of care means that many patients with severe acute brain injury are kept in a medically induced coma during the early stages of recovery. This raises an interesting question about whether the patients in this study were truly comatose or whether their level of awareness reflected the effects of sedatives and other medications (e.g., opioids).
We aimed to address this question by administering the GCS before and after sedation was paused during the EEG assessment. Only Patient 2 exhibited notable changes in behaviour after sedation was withdrawn (as described in Section 4.2 and displayed in Table 2). As such, it was impossible to know from the GCS whether the remaining four patients were truly comatose, experiencing residual effects of sedation, or whether they were conscious but incapable of responding. Alternatively, the results of the CorrCA suggested that both Patient 2 and Patient 4 could process the narrative of “Taken” while off sedation and, accordingly, were awake and aware during the task. While we cannot be certain about the true cognitive states of the remaining patients, as null findings do not necessarily indicate a lack of awareness, these results suggest that the “Taken” task and the CorrCA can be used to identify early markers of residual cognition in behaviourally non-responsive ICU patients.

Finally, the issue of primary versus secondary brain injury should be explored in more detail. Five of the six patients who underwent EEG assessment in this study were admitted to ICU after cardiac arrest, not severe brain injury per se (e.g., trauma, stroke). Although cardiac arrest does not necessarily cause significant neurological damage, we have strong evidence to suggest that these patients did experience secondary anoxic brain injury as a result. First, medical charts indicated that each of these patients experienced a loss of consciousness during their arrest. This strongly suggests a sustained, severe lack of oxygen in the brain and, consequently, some degree of anoxic injury. Second, multiple patients received therapeutic hypothermic treatment in ICU to limit post-anoxic encephalopathy (Beccaria et al., 2010; Nolan et al., 2003). Although this can be administered as a preventative measure before a full neurological investigation is complete (e.g., MRI or CT scan), therapeutic hypothermic treatment is typically used when the severity of the arrest suggests imminent anoxic injury. Lastly, all the patients in this study were at most, minimally responsive upon admission to ICU. Remaining behaviourally non-responsive following a return of spontaneous circulation can indicate anoxic brain injury, though comorbidities like shock may also be a factor (Jozwiak et al., 2020).
4.4.4 Conclusion and future Directions

Overall, we found moderate support that the EEG “Taken” paradigm can be used to detect covert cognitive function in behaviourally non-responsive ICU patients. By combining three analytic techniques, we were able to: 1) identify patients who showed neural evidence of preserved covert cognitive function despite remaining behaviourally non-responsive, 2) differentiate survivors from non-survivors through high-frequency EEG connectivity, and 3) verify that the task is recruiting many of the same cortical areas observed in Study 1 and in fMRI (Laforge, Gonzalez-Lara, et al., 2020; Naci et al., 2015).

One significant limitation of this study is its small sample size (Note: the COVID-19 pandemic and subsequent lockdown measures effectively stopped patient screening and recruitment for this study). Although the CorrCA was designed to assess neural function in individual patients, substantially larger cohorts of patients would be required to replicate the group-level effects reported here. Future studies should aim to recruit many patients across multiple age groups, etiologies, and critical care centers to determine whether the results presented in this study reliably predict outcome after severe brain injury. Additionally, we did not collect physician prediction of outcomes in this study. This limits our ability to compare these results to behavioural assessments and physician expertise. Collecting this data will be crucial to validate that the “Taken” task, and the analytic techniques presented here, perform as well or better than standard clinical measures alone (Duclos et al., 2020). If this is the case, the “Taken” paradigm may provide a powerful bedside assessment of neural and cognitive function for patients with severe acute brain injury.
References


https://doi.org/10.1016/S0079-6123(09)17704-X

https://doi.org/10.3389/fnhum.2014.00950

https://doi.org/10.3389/fneur.2020.00335

https://doi.org/10.1016/j.medine.2015.08.002


Chapter 5

5 General Discussion

4.5 Summary and Key Findings

Establishing awareness in patients with severe brain injury is a considerable challenge. Standardized behavioural assessments remain the gold standard in critical care and outpatient settings (Bagnato et al., 2017; Giacino et al., 2009). However, these are limited in precisely the cases where conscious awareness remains indeterminate. Many patients with acute and chronic disorders of consciousness (DOC) experience significant motor impairments. This critically reduces the sensitivity of behavioural assessments and, thus, their diagnostic and prognostic accuracy (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009; Wang et al., 2020). Assessments of awareness that use neuroimaging technologies like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) offer a powerful alternative to clinical behavioural measures (Fernández-Espejo & Owen, 2013; Owen, 2013; Owen & Coleman, 2007).

Recent years have seen the rapid development of many brain-based proxies of command-following (Cruse et al., 2011; Monti et al., 2010; Naci et al., 2013; Owen et al., 2006) as well as methods to investigate perception and certain cognitively mediated functions at the neural level (Berlingeri et al., 2019; Bruno et al., 2010; Kondziella et al., 2016; Schiff, 2006). Neural assessments have drastically improved the detection of awareness in behaviourally non-responsive individuals. However, many are not well suited to the specific impairments of patients with severe brain injury, and few techniques can speak to the conscious experience of DOC patients. On the other hand, neural assessments that use naturalistic stimuli—like the ones developed by Naci et al. (2014, 2015)—can be used to infer visual, auditory, and “higher-order” executive processing of complex stimuli from single-trial recordings.

The primary goal of this thesis was to develop and validate an EEG version of Naci et al.’s fMRI movie paradigms (2014, 2015) to assess cognitive function through inter-subject correlations (ISCs) in patients with chronic and acute DOC. In contrast to fMRI,
EEG is a low-cost and portable neuroimaging device that is widely available in clinical settings, making it ideal for patients with severe brain injury. However, the limited spatial resolution of EEG required a different method to calculate ISCs, both at the group level and for individual subjects. The study presented in Chapter 2 described the specific experimental design for our EEG assessment, the computational procedures we used for calculating ISCs, and the validation steps we performed to ensure that EEG ISCs reliably captured executive processing of the movies (Cohen & Parra, 2016; Cohen et al., 2017; Dmochowski et al., 2012).

In that study, we demonstrated that EEG could capture ISCs between participants during “Bang! You’re Dead” and “Taken” and that they were statistically robust at the single-subject level—a necessary condition for any assessment designed for DOC patients. We also found that the time course of ISCs were significantly correlated to suspense ratings for both intact movies, but not for the scrambled versions. Combined with the source reconstruction of the frontoparietal executive network during the intact version of “Taken”, these results suggested that our EEG ISCs analyses captured similar neural processes described by Naci et al. (2014, 2015). When we applied this paradigm to a cohort of 13 patients with DOC, we found that 25% and 30% of patients produced a pattern of neural activity that was significantly correlated with healthy controls’ during “Bang! You’re Dead” and “Taken”, respectively. While significant ISCs with controls do not provide definitive evidence of conscious awareness per se, they provide strong evidence of the preserved perceptual and cognitive functions that support it (Boly et al., 2017; Naci et al., 2014). Moreover, this estimate (25 - 30% of patients) is in the same range as those presented in previous studies, despite using a different assessment technique (Kondziella et al., 2016; Monti et al., 2010)—further strengthening the validity of these results.

Chapter 3 explored whether the EEG “Taken” paradigm—the task with the highest proportion of patient responders in Chapter 2—could be extended to non-English speaking populations of DOC patients. The motivation for this study was to provide normative ISCs data from a sample of French-speaking individuals during a translated (to French) version of the “Taken” audio. In doing so, we hoped to establish a benchmark of
ISCs in this new sample for later use in DOC patients across Canada. Here, we found that the French version of “Taken” produced comparable degrees of ISCs as the English version but at different time points throughout the audio; both versions produced a similar frequency of significant ISCs throughout the audio, but the periods in which they occurred varied between languages. However, we determined that this effect was driven by a consistent timing offset between the two versions of the audio rather than intrinsic differences between the narratives themselves. Overall, these results support the use of the translated “Taken” paradigm to assess perceptual and executive processing in cohorts of French-speaking DOC patients.

In Chapter 4, we examined the feasibility of using the EEG “Taken” paradigm in critical care settings. Here, we aimed to determine whether we could detect neural markers of perceptual and cognitive function in a sample of acutely comatose patients and evaluate the prognostic utility of our assessment. In this study, we presented the intact and scrambled versions of “Taken” to patients while they were receiving continuous pharmacological sedation and again after sedation was withdrawn. This enabled us to calculate the differences in ISCs, functional connectivity, and source-localized EEG between conscious states and examine whether the degree of change predicted later outcomes.

After withdrawal of sedation, two of the five patients produced significant ISCs with controls during the intact version of “Taken”, but only one survived. Conversely, one patient who did not show any significant ISCs with controls survived, providing mixed evidence of the prognostic value of ISCs in this population. We found that variability in group-level functional connectivity during the task was marginally associated with survival from acute brain injury. Specifically, the differences in high-frequency EEG connectivity between audio conditions were smaller—neural activity was more stable—in patients who would survive their injury. Relative to patients who would not survive, this pattern more closely approximated what we observed in healthy control participants. Finally, source localized EEG activity revealed the predicted frontoparietal-temporal divide between the intact and scrambled versions of “Taken” in acutely comatose
patients. However, cortically reconstructed activity was not associated with outcomes in this sample.

Over three studies, we developed, tested, and validated an EEG analysis technique that enables us to assess perceptual and cognitive processing in patients with chronic and acute DOC. We have also demonstrated that this technique is suitable for different populations of DOC patients (i.e., English or French speaking; chronic or acute) and can account for the specific perceptual abilities of individual patients (i.e., audio-visual, audio only). Finally, while the prognostic efficacy of the EEG “Taken” paradigm remains to be determined, we found marginal evidence that a multi-method EEG analysis could uncover clinically meaningful patterns of neural activity that may inform outcome predictions in patients with severe acute brain injury.

### 4.6 Contributions to the Field

Despite the large and growing repertoire of neural assessments for patients with DOC, our EEG movie task, ISCs analysis protocol, and applications described in this thesis contribute to the broader literature in three unique ways. First, by successfully adapting the movie paradigms presented by Naci et al. (2014, 2015) for EEG, we have made this assessment a viable option for a considerably larger proportion of patients with chronic and acute DOC. As stated previously, EEG is a cost-effective and portable neuroimaging device that is widely available (Cruse et al., 2011, 2012; Naci et al., 2012). As such, it is much more likely that researchers and clinical staff can access the necessary tools for this assessment compared to those required for fMRI. Furthermore, the results of the numerous validation steps outlined in Chapter 2, while not unique in themselves—ostensibly replicating the findings from Naci et al.—strongly support the validity of this EEG-based version of the paradigm.

However, we were not the first to propose using naturalistic stimuli and EEG to assess patients with DOC. Iotzov et al. (2017) used a similar ISCs analysis to compare neural activity in healthy controls and patients with chronic DOC during two types of naturalistic speech stimuli (both presented forward and backward). They found that, as a group, patients with DOC exhibited lower ISCs overall than healthy controls and that
ISCs scale with behavioural diagnosis. Additionally, in healthy controls, ISCs were
significantly higher during the forward speech condition than backward speech, but ISCs
in patients did not differ between conditions. While these findings are informative, there
are key differences between Iotzov and colleagues’ assessment and our own. Iotzov and
colleagues did not design their task to assess cognitive function in individual DOC
patients; they examined group-level differences in ISCs that varied by clinical status (i.e.,
healthy controls, DOC patients) and behavioural diagnosis. They also used ISCs to
corroborate, rather than inform, behavioural diagnosis in patients with DOC. For these
reasons, our assessment—specifically designed to supplement behavioural diagnosis in
*individual* patients—its validation procedures (e.g., permutation testing, correlations with
suspense, source localized activity), and findings in DOC patients remain unique.

Second, we further expanded the applicability of the naturalistic auditory assessment by
establishing a normative baseline of healthy control ISCs during a French version of
“*Taken*”. Few studies have investigated whether neural activity evoked by naturalistic
stimuli differs across languages. If, as we assume, much of the observed neural activity
(especially in frontal and parietal cortices) is driven by the semantic content of the audio
narrative rather than its physical/acoustic properties, then we would expect considerable
overlap between the two language versions. One such study by Honey et al. (2012) found
minimal differences in hemodynamic ISCs during the same audio story presented in
English to English-speaking participants and Russian to Russian-speaking participants.
Honey and colleagues suggested that, despite the structural differences between the two
languages, the shared meaning of the story produced spatially similar ISCs across groups.
Building off this work, with a focus on Canadian cohorts of chronic and acute DOC
patients, the study presented in Chapter 3 provided a direct comparison of EEG ISCs
between English and French versions of “*Taken*”. To the best of our knowledge, this is
the only study of its kind to do so.

Third, in Chapter 4, we demonstrated that the EEG “*Taken*” task may be clinically
informative for patients with severe acute brain injury, particularly when using a multi-
method analysis technique. Neuroimaging research on acute DOC has rapidly accelerated
in recent years, with many studies investigating the efficacy of established neural
assessments in the early stages of severe brain injury. These include covert command following, hierarchical measures of perceptual function, and naturalistic processing tasks that use music or speech (Chatelle et al., 2020; Edlow et al., 2017; Edlow & Naccache, 2021; Sokoliuk et al., 2021). Identifying neural correlates of conscious awareness in the early stages of acute brain injury is critical for accurate diagnosis—especially when behavioural markers are absent or unreliable. However, prognostication of outcome plays a key role in guiding the course of treatment and determining whether to withdraw life-sustaining therapy (WLST). To the latter, naturalistic assessments of patients with acute DOC improve prognostic accuracy relative to behavioural measures alone (Chatelle et al., 2020; Sokoliuk et al., 2021; Threlkeld et al., 2018).

Relative to other methods, our ISCs analysis has the advantage of directly comparing an individual patient’s neural activity during “Taken” to healthy controls while also accounting for the variability in their EEG using permutation statistics. This technique capitalizes on the known spatiotemporal extent of frontoparietal network activity during “Taken” (Chapter 2) but allows us to flexibly accommodate individual differences in EEG activity, which is ideal for patients with severe brain injury (Bareham et al., 2019; Cruse et al., 2011; Engemann et al., 2018). Moreover, by presenting both the intact and scrambled versions of the audio, we can differentiate ISCs related to auditory (scrambled) and executive (intact) processing—thereby increasing the specificity of the assessment by hierarchically indexing neural functions.

Finally, our multi-method analysis protocol, combined with contrasts between levels of sedation, is unique in the acute DOC population. Previous studies have primarily focused on a single neural measure (e.g., BOLD activation) or state of awareness (e.g., patients off sedation). Our approach, however, enables multiple levels of analysis and captures different dimensions of neural activity during the task; ISCs reflect the similarity of neural activity between patients and controls; inter-electrode coherence quantifies the contributions of different EEG frequency bands during the audio; cortical source reconstruction uncovers the neural generators of EEG activity. The manipulation of level of sedation also provided additional contrasts with which to compare across patients and groups—namely, examining the magnitude of change within each analysis type (Duclos
et al., 2020, 2021). While potentially meaningful on their own, each measure and contrast can inform the others to create a detailed description of neural function among patients. For example, while off sedation, patients with poor outcomes showed higher variability in connectivity among Beta and Gamma frequency bands during the task. This may have affected ISCs among patients who did not survive, as increased variability can heighten thresholds for statistical significance when using permutation testing (Nichols & Holmes, 2002). While it was beyond the scope of this study to fully explore these relationships or their prognostic value, it provides a novel model for EEG assessments of naturalistic processing in patients with acute DOC.

4.7 Limitations and Recommendations for Future Research

4.7.1 Practical Concerns and Theoretical Issues

One of the most significant limitations of this thesis pertains to the sample size of acutely comatose patients in Chapter 4. This study commenced weeks before the beginning COVID-19 pandemic and subsequent restrictions, significantly affecting patient enrollment. Nevertheless, we did manage to establish the feasibility of applying the “Taken” paradigm in patients with severe acute brain injury, but our findings, particularly those at the group level, should be interpreted with caution. Our ISCs analysis is designed to assess individual DOC patients and, as such, was not necessarily affected by the small sample size. However, any interpretation of significant ISCs relative to outcomes is severely limited.

The same is true for the results from our functional connectivity and source localization analyses as well. While there is evidence of disrupted EEG activity in patients with acute DOC (Chatelle et al., 2020; Lehembre et al., 2012; O’Donnell et al., 2021), we found only marginal differences in high-frequency variability between audio conditions when comparing patients with good and poor outcomes. Given the novelty of this particular contrast and the small sample size, it is difficult to reconcile this effect with those in the broader literature. Still, the implications of these results—that is, patients with good outcomes showed functional connectivity profiles that more closely resembled healthy controls—are consistent with the hypotheses guiding our ISCs analysis and many neural
assessments of DOC patients. Likewise, the prognostic efficacy of our source localization procedure remains unclear. However, the differential activation of frontoparietal and temporal regions during the intact and scrambled versions of “Taken” does support the use of this assessment in acutely brain-injured patients.

Concerning patient outcomes, there is a crucial difference between natural death and WLST. In Chapter 4, we coded outcomes as a binary variable to group patients who survived from those who did not. This conflates natural physiological processes and medical decision-making. WLST can be initiated for multiple reasons other than imminent death; high probability of significant cognitive impairments, protracted length of recovery, or personal beliefs surrounding medical interventions can play a significant role in the decision to WLST (Barnato et al., 2012; Lee et al., 2020). Furthermore, natural death in hospital may occur for reasons other than a patient’s primary injury. For example, Patient 2 in Chapter 4 passed away from complications of pneumonia unrelated to her initial cause of admission. For our purposes, however, separating patients with poor outcomes by cause of death would have further reduced the sample size of this group and, subsequently, the (already limited) statistical power of our analyses.

In a similar vein, the low statistical power of the study in Chapter 4 limited comparisons between our EEG analyses and relevant clinical measures. Indeed, we obtained Glasgow Coma Scale (GCS; Teasdale & Jennett, 1976) scores for each of the five patients included in this study, both while on and off pharmacological sedation. However, the restricted range and number of GCS scores available from this sample hindered our ability to discern meaningful relationships between behavioural scores and EEG. We also planned to obtain Glasgow Outcome Scale-Extended (Teasdale et al., 1998) scores for those who recovered, but patient follow-ups were also affected by the COVID-19 pandemic. These comparisons are crucial to establish the utility of neural assessments in acutely comatose patients and are the only way to determine their prognostic efficacy in this population. Future work, therefore, should prioritize evaluating the correspondence (or lack thereof) between neural assessments and clinical behavioural measures of awareness and eventual outcome after severe acute brain injury.
4.7.2 Methodological Considerations

In general, naturalistic assessments of cognitive function in patients with DOC assuage many of the constraints of active tasks and conventional passive paradigms (Naci et al., 2014, 2015, 2018). However, the specific methodology outlined in this thesis has notable limitations. Assessments of awareness in patients with DOC, whether behavioural or neural, benefit from repeat applications; patients’ arousal and cognitive abilities fluctuate over time, and accurate appraisals of their true level of function may require multiple assessments. Naturalistic movie tasks, especially those that rely on narrative properties like suspense, lose their ability to engage viewers/listeners and sustain their attention upon repeat presentations. Dmochowski et al. (2012) found that ISCs among healthy participants decreased considerably during a second viewing of “Bang! You’re Dead”, owing to increased predictability of its events. Likewise, Ki and colleagues (2016) reported a significant decrease in ISCs when participants attended to a secondary task. Therefore, our EEG assessment is not ideal for routine assessments. Future work in this area would benefit from including multiple movies and stories—each with their own normative ISCs from healthy controls—to capture executive processing in individual patients over time.

Another limitation of this approach relates to the number of EEG components available for analysis relative to the one we used for assessment. The correlated components analysis (CorrCA) extracts $N - 1$ (where $N$ is the number of EEG sensors) topographic components that reflect different patterns of EEG activity and underlying neural processes (Dmochowski et al., 2012; Ki et al., 2016). Across the three studies presented in this thesis, we only examined the component that maximized the correlation between participants (i.e., the top-ranked component). Although we found strong evidence that the top-ranked components in each movie condition captured task-relevant neural processes (e.g., frontoparietal executive function during “Taken”; source localization in Chapter 2), these are likely distributed across multiple components. As such, analyzing the time courses and potential cortical sources of multiple CorrCA components, whether individually or combined, could improve our ability to detect neural markers of executive processing in patients with DOC.
Similarly, the way we implemented the CorrCA across these studies may not be sufficiently sensitive to the complex dynamics of electrophysiological activity during movie tasks. As noted in Chapter 4, CorrCA only accounts for fluctuations in EEG amplitude over time; it does not index more complex signal dynamics like frequency or phase. This was advantageous for a preliminary assessment of the feasibility of this approach, as presented here, but does collapse across dimensions of the EEG data which undoubtedly capture meaningful aspects of narrative processing. Fluctuations in EEG frequency power throughout the movies would most likely correspond with dynamic changes in the physical features of the stimuli like brightness, motion, or loudness, as well as higher-order properties like speech and, of course, the narrative. By these tracking frequency dynamics—either by calculating the CorrCA within specific frequency domains or employing a time-resolved version of inter-electrode coherence—we may be able to simultaneously assess multiple levels of perceptual and cognitive function in patients using a single stimulus.

Regarding functional connectivity, the approach described in Chapter 4 could also be improved to more accurately describe the neural dynamics of acutely comatose patients during the “Taken” task. Inter-electrode coherence is a relatively simplistic measure of functional connectivity. Mathematically, coherence closely resembles cross-correlations but is calculated on the frequency rather than the time domain. In this way, it is less resistant to the codependences intrinsic in EEG data and to instantaneous (and likely spurious) interactions between disparate areas. More sophisticated connectivity measures like weight phase lag index and the imaginary part of the coherence method are more robust to these effects and account for volume conduction (i.e., accounting for distance between electrodes; Bastos & Schoffelen, 2016; Bowyer, 2016).

Similarly, there are many different methods to source localize EEG signals; minimum norm estimates, low-resolution electromagnetic tomography, dipole modelling each have their own advantages and limitations (Tadel et al., 2011). Irrespective of the specific method used, the accuracy of cortical estimates generally improves when using second-order analyses (Asadzadeh et al., 2020; Michel & Murray, 2012; Tadel et al., 2011). Specifically, source estimation procedures of pre-processed EEG data provide a coarse
estimate of its cortical generators and typically include some combination of noise and spurious solutions across vertices. Applying additional analyses, like functional connectivity, can ameliorate some of these concerns for the reasons outlined above. Future work would benefit from moving beyond simple source estimation procedures presented in Chapters 2 and 4 and, instead, include second-order analyses to improve the precision of the solutions in healthy controls and patients with DOC.

4.8 Concluding Statements

Functional neuroimaging has revolutionized the assessment, diagnosis, and prognosis of patients with chronic and acute DOC. Neural assessments are now recommended to supplement standardized behavioural measures in cases where awareness cannot be established after severe brain injury (Giacino et al., 2018). However, these assessments vary considerably by type (e.g., fMRI, EEG) and objective. Naturalistic paradigms, like the ones developed by Naci et al. (2014, 2015), are unique in their ability to characterize the conscious experience of individual patients, in addition to perceptual function and awareness. The EEG-based movie protocol presented in this thesis capitalizes on the robust effects of naturalistic processing while also making this assessment technique more accessible to researchers, clinicians, and patients alike. It is our hope that this assessment, or updated versions of it, will be deployed widely across critical care and outpatient centers as an alternative to previously established paradigms. While novel technologies are being developed to establish functional communication in behaviourally non-responsive patients (Abdalmalak et al., 2017; Chatelle et al., 2012) and therapeutic interventions may one day cure DOC altogether (Caën et al., 2021; Monti et al., 2016), in the interim, our EEG protocol provides a rapid, low-cost, and effective tool to detect neural markers of preserved awareness in patients with chronic and acute DOC.
References


Appendices

Appendix A: Ethics Approval.

Western Research

Date: 13 May 2021
Tie: Adrian Owen
Project ID: [Redacted]

Study Title: EEG assessment of sensory and cognitive functioning in patients with disorders of consciousness

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 08/June/2021
Date Approval Issued: 13/May/2021
REB Approval Expiry Date: 17/May/2022

Dear Adrian Owen,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH-GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number [Redacted]

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Date: 17 March 2021

To Dr. Adrian Owen

Project ID: [redacted]

Study Title: Electrophysiological markers of conscious processing

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 06/April/2021

Date Approval Issued: 17/Mar/2021

REB Approval Expiry Date: 06/Apr/2022

Dear Dr. Adrian Owen,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number [redacted].

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Date: 26 October 2021

To: Dr. Adrian Owen

Project ID: [redacted]

Study Title: Establishing Neurophysiological Evidence for the Treatment of Brain Injury in Intensive Care Units

Study Sponsor: The University of Western Ontario

Application Type: HSREB Amendment Form

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 02 Nov/2021

Date Approval Issued: 26 Oct/2021

REB Approval Expiry Date: 25 Jul/2022

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Dear Dr. Adrian Owen,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Acknowledged:

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REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH/GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB [redacted].

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer (psargeant@uwo.ca) on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Supplementary Figure 1. Factorial ANOVA results for the cross-projection analysis. We performed a 2x2 factorial ANOVA to investigate potential interaction effects of our cross-projection analysis, where we computed inter-subject correlations (ISCs) for the data in one condition using the components from the other (e.g., computing ISCs for the scrambled audio using the intact audio component). A) The 2x2 factorial ANOVA revealed a significant main effect of projection type, $F(1,12) = 20.83, p = 7e^{-4}$, but no interaction, $F(1,12) = 0.73, p = 0.41$, for the intact or scrambled versions of “Bang! You’re Dead”. B) Similarly, only the main effect of projection type, $F(1,14) = 73.12, p = 6.3e^{-7}$, was significant during the intact and scrambled version of “Taken”.
Supplementary Figure 2. Correlations between temporal ISCs and suspense ratings for the intact and scrambled versions of “Bang! You’re Dead”. A) The time course of temporal ISCs (red) for the intact version of “Bang! You’re Dead” were significantly correlated to the suspense ratings for the movie (blue), $r = 0.179, p = 6e^{-3}$. B) We did not find a significant correlation between the temporal ISCs (red) and the intact suspense ratings (blue) for the scrambled version of “Bang! You’re Dead”, $r = 0.045, p = 0.486$. Note: Suspense ratings were scaled down to improve visualization, but correlations were computed on unscaled values.
Supplementary Figure 3. CorrCA component topographies from healthy controls during the intact and scrambled versions of “Bang! You’re Dead” and “Taken”. The component topography calculated on the EEG data from the intact version of “Bang! You’re Dead” (left, top) showed a considerable degree of similarity with the scrambled component (right, top). However, the component from the intact version of “Taken” (left, bottom) was highly dissimilar to the scrambled component (right, bottom).
Supplementary Figure 4. Correlations between temporal ISCs and suspense ratings for the intact and scrambled versions of “Taken”. A) The time course of temporal ISCs (red) for the intact version of “Taken were significantly correlated to the suspense ratings for the movie (blue), $r = 0.186$, $p = 0.025$. B) Like “Bang! You’re Dead”, the correlation between the temporal ISCs (red) for the scrambled version of “Taken” and its intact suspense ratings (blue) were not statistically significant, $r = 0.107$, $p = 0.20$. 
Supplementary Figure 5. Raw ISCs between patients and healthy controls for the intact version of “Bang! You’re Dead” and “Taken”. A) Raw ISCs between patients (not significant, purple; significant, red) and healthy controls for “Bang! You’re Dead”. B) Raw ISCs between patients (not significant, purple; significant, red) and healthy controls for “Taken”. Absolute ISCs were reported in the manuscript to account for individual differences in dipole orientation (polarity) relative to the group-level component projection.
Curriculum Vitae

Geoffrey Laforge, M.Sc.
Ph.D. Candidate, Psychology - Behavioural and Cognitive Neuroscience
The University of Western Ontario
London, ON. Canada

Post Secondary Education

Sept. 2017 -
Ph.D. Psychology - Behavioural and Cognitive Neuroscience
The University of Western Ontario
Supervisor: Adrian Owen
Expected Spring 2022

Sept. 2015 - 2017
M.Sc. Psychology - Behavioural and Cognitive Neuroscience
The University of Western Ontario
Supervisor: Adrian Owen
Thesis title: Identifying Electrophysiological Components of Covert Awareness in Patients with Disorders of Consciousness

Sept. 2011 - 2015
B.Sc. Psychology
Trent University
Supervisor: Ben Bauer
Thesis title: Crowd(un)sourcing: The Effect of Diffuse Visual Attention on Target Orientation Discrimination

Peer Reviewed Publications


**In Preparation**


### Research Experience

<table>
<thead>
<tr>
<th>Period</th>
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<th>Research focus</th>
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<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 2015 -</td>
<td>Graduate Trainee</td>
<td>Adrian Owen</td>
<td>Electroencephalography, severe brain injury</td>
<td>The University of Western Ontario</td>
<td>London, ON. Canada</td>
</tr>
<tr>
<td>April 2018 - 2019</td>
<td>Patient Coordinator - Owen Lab</td>
<td>Adrian Owen</td>
<td></td>
<td>The University of Western Ontario</td>
<td>London, ON. Canada</td>
</tr>
<tr>
<td>Sept. 2015 – 2016</td>
<td>Research Assistant - Language and Cognition Lab</td>
<td>Nancie Im-Bolter</td>
<td>Developmental executive function, theory of mind</td>
<td>Trent University</td>
<td>Oshawa, ON. Canada</td>
</tr>
<tr>
<td>Sept. 2013 - 2014</td>
<td>Research Assistant - Vision and Cognition Lab</td>
<td>Ben Bauer</td>
<td>Visual processing, attention, psychophysics</td>
<td>Trent University</td>
<td>Oshawa, ON. Canada</td>
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### Clinical Experience

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### Teaching and Professional Experience

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<th>Period</th>
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<tbody>
<tr>
<td>Sept. - Dec. 2021</td>
<td>Teaching Assistant</td>
<td>Psychology as a Natural Science</td>
<td>The University of Western Ontario</td>
</tr>
<tr>
<td>Jan. - April 2021</td>
<td>Teaching Assistant</td>
<td>Cognitive Neuroscience</td>
<td>King’s University College</td>
</tr>
</tbody>
</table>
Sept. 2017 - 2021  Head Teaching Assistant
    Research Methods and Statistical Analysis in Psychology
    The University of Western Ontario
    London, ON. Canada

Sept. 2015 - 2017  Graduate Teaching Assistant - Lecturer
    Research Methods and Statistical Analysis in Psychology
    The University of Western Ontario
    London, ON. Canada

Oct. 2013 - 2015  Teaching Assistant - Finals Marker
    Introduction to Philosophy of Mind
    Trent University
    Oshawa, ON. Canada

**Academic Conferences**

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<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
<th>Talks/Posters</th>
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<tr>
<td>May 19, 2021</td>
<td>1st Canadian Consciousness Research Symposium</td>
<td>Montreal, QC. Canada</td>
<td>Talk: Identifying Neural Markers of Naturalistic Processing in Patients with Severe Acute Brain Injury: A Multi-Method EEG Approach</td>
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<tr>
<td>June 25 - 28, 2019</td>
<td>23rd Meeting of the ASSC</td>
<td>London, ON. Canada</td>
<td>Talk: Using EEG to Detect Neural Markers of Naturalistic Stimulus Processing in Patients with Disorders of Consciousness Association for the Scientific Study of Consciousness</td>
</tr>
<tr>
<td>Mar. 13 - 16, 2019</td>
<td>World Congress on Brain Injury</td>
<td>Toronto, ON. Canada</td>
<td>Poster: Using EEG to Identify Markers of Naturalistic Stimulus Processing in Patients with Disorders of Consciousness</td>
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<tr>
<td>Nov. 3 - 7, 2018</td>
<td>Society for Neuroscience Conference</td>
<td>San Diego, CA. USA</td>
<td>Poster: Identifying Electrophysiological Indices of Covert Awareness in Patients with Disorders of Consciousness</td>
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Mar. 19 - 21, 2018  Traumatic Brain Injury and Concussion Conference
Rotman Research Institute
**Moderated poster:** Identifying Electrophysiological Components of Covert Awareness in Patients with Disorders of Consciousness
Toronto, ON. Canada

Feb. 2 - 3, 2017  Lake Ontario Visionary Establishment
**Poster:** Identifying Electrophysiological Indices of Covert Awareness in Patients with Disorders of Consciousness
Niagara Falls, ON. Canada

**Academic Workshops**

<table>
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<th>Date</th>
<th>Event</th>
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<tr>
<td>Sept. 2 - 7, 2019</td>
<td>Visceral Mind Neuroanatomy Workshop</td>
<td>Bangor University, Bangor, Wales, UK.</td>
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<td>Mar. 7 - 8, 2018</td>
<td>Decoding Mental States using EEG Workshop</td>
<td>Montreal Neurological Institute, Montreal, QC. Canada</td>
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<tr>
<td>April 25 - 29, 2016</td>
<td>Brock University and EEG SHARCNet: EEG Analysis Workshop</td>
<td>Brock University, St. Catharines, ON. Canada</td>
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<tr>
<td>May 7 - 8, 2015</td>
<td>Attention and Conscious Perception Workshop</td>
<td>York University, Toronto, ON. Canada</td>
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**Scholarship and Awards**

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<th>Date</th>
<th>Scholarship/Award</th>
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<tbody>
<tr>
<td>July 2020</td>
<td>Graduate Student Teaching Assistant Award of Excellence</td>
<td>The University of Western Ontario, London, ON. Canada</td>
<td>$50</td>
</tr>
<tr>
<td>July 2020</td>
<td>Richard A. Harshman Scholarship – Statistical Methods</td>
<td>The University of Western Ontario, London, ON. Canada</td>
<td>$1,500</td>
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<tr>
<td>Sept. 2019</td>
<td>Ontario Graduate Scholarship</td>
<td>The University of Western Ontario, London, ON. Canada</td>
<td>$15,000</td>
</tr>
<tr>
<td>Year</td>
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</tr>
<tr>
<td>Sept. 2013</td>
<td>Trent University In-Course Scholarship</td>
<td>Trent University</td>
<td>Oshawa, ON. Canada</td>
</tr>
<tr>
<td>Sept. 2011</td>
<td>Trent University In-Course Scholarship</td>
<td>Trent University</td>
<td>Oshawa, ON. Canada</td>
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