AUDITORY AND VISUAL ERPS AS BRAIN VITAL SIGNS: THE EVOLVING HALIFAX CONSCIOUSNESS SCANNER

by

Carolyn M. Fleck-Prediger

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Abstract

Covert awareness is difficult to detect in patients with cognitive-motor dissociation after severe neurological injury. In order to avoid over-reliance on subjective measures which are error prone, neurological evaluations must include behaviour-based ratings and objective, technology-based measures. The Halifax Consciousness Scanner is an electroencephalography (EEG) based system that delivers stimuli and records a range of Event Related Potentials (ERPs) which can be used to infer sensory, perceptual, attention, memory and language capacities. This dissertation discusses disorders of consciousness (DoC), details issues pertaining to prognostication and differential diagnosis, and reviews present and emerging diagnostic options. The first paper reviews recent literature regarding the clinical utility of evoked and cortically derived ERPs for evaluating DoC. The second paper describes a pilot study conducted with the auditory HCS contrasting a patient's ERP profile before and after intensive speech-language intervention. P300 responses remained stable, while the amplitude of the N400 improved with concurrent gains in language comprehension. The third paper details the clinical deployment of the auditory HCS for trial at various points of care across Canada. Twenty-eight survivors of severe brain injury were tested with the auditory version of the HCS. The latency of the HCS derived P300 responses correlated with scores on clinical scales. The fourth paper discusses the development of a visual ERP paradigm that may be used in conjunction with the HCS. In this study on healthy controls, the stimuli were delivered via the Raspberry Pi 3 personal computer and the data were collected with the MUSE portable headset. Robust P300 responses were detected in response to familiar, personally relevant stimuli. This dissertation adds to existing literature by summarizing the current methodologies for assessing DoC while highlighting the utility and limitations of long latency ERPs. It discusses point of care evaluations with the Halifax Consciousness Scanner and introduces the development of a language and literacy-free visual paradigm to complement the existing auditory stimuli.

Preface

This thesis is an original work by Carolyn M. Fleck-Prediger. All research projects received ethics approval from the University of Alberta Human Research Ethics Board. Chapters 1 (Introduction) and 2 (Summary of Related Work) have not been published elsewhere. Chapter 3 will be submitted for publication as Fleck-Prediger, C.M., D'Arcy, R.C., Gray, D.S., Fujiwara, E., & Dick B.D. Traces of Consciousness: Reviewing the Utility of Evoked and Long Latency Event Related Potentials in Adults with Pervasive Disorders of Consciousness after Brain Injury. Chapter 4 has been published as Fleck-Prediger, C., Hajra, S. G., Dick, B. D., Gray, D. S., Liu, C.C., Petley, L., & D'Arcy, R. C. (2015). Clinical Applications of the Halifax Consciousness Scanner: Tracking Recovery in a Severely Brain Injured Patient. *Int Neurotrauma Lett*. (Pro00030554). Chapter 5 has been published as Fleck-Prediger, C.M., Ghosh Hajra, S., Liu, C.C., Gray, D.S., Weaver, D.F., Gopinath, S., Dick, B.D. & D'Arcy, R.C. (2018). Point of Care Brain Injury Evaluation of Conscious Awareness: Wide Scale Deployment of Portable HCS EEG Evaluation. *Neuroscience of consciousness*, *2018*(1), niy011 (Pro00030554). For Chapters 4 and 5, I was responsible for recruiting patient participants, ensuring informed consent, assisting with data collection/analysis/interpretation, and drafting the manuscript. Chapter 6 has been submitted for publication as Fleck-Prediger, C.M., Dick, B.D., Liu, C.C., Ghosh Hajra, S., Kusiak, J.W.P., Tayem, A., Wilkinson, M., Gray, D.S., Fujiwara, E., D'Arcy R.C.N. & Kyle E. Mathewson. P300 to Familiar and Unfamiliar Faces and Places (PRO00044319). I was responsible for conceptualizing the protocol, creating the stimuli, recruiting healthy controls, obtaining informed consent, and assisting with data acquisition/analysis/ interpretation, and drafting the manuscript.

Acknowledgements

Where to start? As a SLP specializing in sub-acute, moderate-severe brain injury, I took a leap of faith in returning to university after many years of clinical practice. Indeed, there were times when I questioned the choice but in retrospect, I am extremely grateful for the journey and treasure my expanded competencies. My primary supervisor, Dr. Bruce Dick, guided me through the process and I would have lost my way without him acting as beacon of light. Drs. Ryan D'Arcy and Shaun Gray - thank you for believing in me, pushing me (way!) outside of my comfort zone, and standing by me. Dr. Esther Fujiwara, thank you for stepping in and bringing a wealth of knowledge.

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Finally, to my immediate family, extended family and friends – thank you for your patience and love. I know "sharing me" with the demands of this training has been difficult. I will never forget what you have sacrificed to enable this journey. You are all amazing and I am so blessed to have each and every one of you in my life. Thank you for staying the course. Love you all to the moon and back.

Table of Contents

Table of Contents

List of Abbreviations

BAEP	Brainstem Auditory Evoked Potential
BCI	Brain Computer Interface
BOLD	Blood-Oxygenation-Level Dependent
BVS	Brain Vital Sign
CLIS	Complete Locked-In State
CLOCS	Comprehensive Levels of Consciousness Scale
CMD	Cognitive Motor Dissociation
CMS	Cortically Mediated State
CNS	Coma/Near Coma Scale
CRS-R	Coma Recovery Scale-Revised
CS	Conscious State
DBS	Deep Brain Stimulation
DCA	Detecting Cognitive Activity
DoC	Disorder of Consciousness
DOCS	Disorders of Consciousness Scale
EBS	Elemental Brain Score
EEG	Electroencephalography
EMCS	Emergence from Minimally Conscious State
ENE	Early Negative Enhancement
EOG	Electro-oculograms
EP	Evoked Potential
ERP	Event-Related Potential
EPSP	Excitatory Post Synaptic Potential
FIM	Functional Independence Measure
FOUR	Full Outline of Unresponsiveness Score
fMRI	Functional Magnetic Resonance Imaging
fNIRS	functional Near Infrared Spectroscopy
GCS	Glasgow Coma Scale

List of Abbreviations

GCS-R	Glasgow Coma Scale-Revised
GLS	Glasgow-Liege Coma Scale
GNT	Global Network Theory
GPi	Globus pallidus interna
GWT	Global Workspace Theory
HC	Healthy Controls
HCS	Halifax Consciousness Scanner
iCWT	Inverse Continuous Wavelet Transform
IPSP	Inhibitory Post Synaptic Potential
INNS	Innsbruck Coma Scale
ISI	Inter-stimulus Interval
IIT	Integrated Information Theory
LIS	Locked-In State
LOC	Level of Consciousness
LOEW	Loewenstein Communication Scale
LPP	Late Positive Potential
MBT	Motor Behaviour Tool
MBT-r	Motor Behaviour Tool-revised
MCS	Minimally Conscious State
MCS-	Minimally Conscious State Minus
MCS+	Minimally Conscious State Plus
MEG	Magnetoencephalography
MLAEP	Middle Latency Auditory Evoked Potential
MMN	Mismatch Negativity
MRI	Magnetic Resonance Imaging
MSN	Medium Spiny Neurons
n-P3	Novelty P300
PC	Perturbational Complexity
PCI	Perturbational Complexity Index
PET	Positron Emission Tomography
PPN	Prefrontal Parietal Network

List of Abbreviations

PSP	Post-synaptic Potential
REM	Rapid Eye Movement
RLS85	Swedish Reaction Level Scale-1985
QEEG	Quantitative EEG
SEP/SSEP	Somatosensory Evoked Potential
SMART	Sensory Modality Assessment Technique
SON	Subject’s Own Name
SVM	Support Vector Machine
TTD	Thought Translation Device
UWS	Unresponsive Wakefulness Syndrome
VEP	Visual Evoked Potential
VS	Vegetative State
WHIM	Wessex Head Injury Matrix
WNSSP	Western Neuro Sensory Stimulation Profile

List of Tables

Chapter 1

Chapter 2 No Tables

Chapter 3

Chapter 4 No Tables

Chapter 5

Chapter 6

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5:

Chapter 6

Chapter 7

Chapter 1: General Introduction

The management of disorders of consciousness has spurred intense debate as this is an area where the natural sciences of medicine and the social sciences of ethics and law intersect, and conflicting perspectives are common. The unfortunate case of Terri Schiavo, a patient diagnosed with Unresponsive Wakeful Syndrome (UWS) after cardiac arrest and subsequent massive brain damage (Fins, 2008), exemplifies the polarity and intensity of opinions regarding the right to live, the right to die, and the appropriateness of providing futile medical care (Baker, 2016; Brayton & Sinnott-Armstrong, 2016). Schiavo's husband and legal guardian Michael petitioned to withhold a life-sustaining procedure but was vehemently opposed by Schaivo's parents (Baker, 2016). The case became a public spectacle, with raging emotions fueling the debate. The dispute however, goes beyond decisions regarding life and death, and controversy has arisen over the ethical obligation to provide appropriate care and intervention given limited healthcare resources. Since consciousness cannot be directly observed, covert awareness is difficult to detect in patients with cognitive motor dissociation after severe neurological injury. Graham (2018) argues that in common practice, our appraisal of the subjective state of a non-responsive patient is almost entirely guesswork. He asserts that it is ethically necessary to evaluate all unresponsive patients for cognitive motor dissociation (CMD) with appropriate technology. Schiff (2015) describes CMD as those who cannot purposefully move but demonstrate brain activity associated with intentional thinking and remembering. He stresses the importance of identifying these individuals and finding ways to help them.

To provide a common frame of reference for the diagnosis and treatment of persons with DoC, three ascending levels of disordered consciousness have been adopted: coma; the vegetative state (VS) or unresponsive wakeful state (UWS); and the minimally conscious state (MCS). Coma is a state of unarousable unresponsiveness with no evidence of self or environmental awareness (Plum & Posner, 1982). In coma, no spontaneous eye opening or sleep/wake cycles are apparent. Transition to the VS/UWS marked by periodic eye opening and sleep wake cycles without purposeful or voluntary behaviour and without evidence of language comprehension or expression. Patients who transition to MCS demonstrate minimal but distinct behavioural evidence of self or environmental awareness and the Aspen Workgroup has specified that to qualify as MCS (Giacino et al., 2002) patients must demonstrate at least one of the following a) clear and reproducible simple command following, b) gestural or verbal yes/no responses (regardless of accuracy); c) intelligible verbalization; or d) movements or affective behaviours in response to stimuli. To emerge from MCS (EMCS), patients must reliably demonstrate interactive communication (i.e. accurate yes/no) or functional object use (Bruno, Vanhaudenhuyse, Thibaut, Moonen & Laureys, 2011).

1.1 Prevalence of Disorders of Consciousness

The rate of acquired brain injury continues to rise in both Canada and the United States and patients are more apt to survive after severe neurological injury given advances in critical care medicine (Rao, McFaull, Thompson, & Jayaraman, 2017). However, the ratio of severe brain injury to mortality varies between and within countries due, in large part, to the availability and investment in care and treatment (Sazbon & Dolce, 2002 as cited in Beaumont and Kenealy, 2005). In a large Canadian study involving 720 patients with traumatic brain injury across six level one trauma centres, Turgeon and colleagues (2011) demonstrated that thirty-two percent of patients with severe brain injury died in hospital and 70% of these deaths resulted from the withdrawal of life-sustaining treatment, often within a few days of their injury and before their prognosis was certain. The mortality associated with the withdrawal of life-sustaining therapy varied across clinical sites from 10.8 to 44.2% and the choice to withdraw or maintain life sustaining intervention was often based on the opinion of the treating clinician as to potential outcome. In 1994, the Multi-Society Task Force estimated the prevalence of vegetative state in adults to be between 10 000-25 000 people in the United States. Pisa, Biasutti, Drigo, and Barbone (2014) conducted a systematic review in an attempt to ascertain a current estimate of the prevalence of unresponsive wakeful state and minimally conscious state. Unfortunately, the group was unable to provide a summary estimate of prevalence due to the limited number of studies and the degree of heterogeneity between the studies. Five cross-sectional surveys were found for vegetative state and only one of those considered minimally conscious state separately. The prevalence ranged from .2 to 3.4

per 100 000 people for vegetative state and 1.5 per 100 000 people for minimally conscious state. For vegetative wakeful state, the Netherlands was on the low end of that range (i.e. .1-.2) (van Erp et al., 2015). In addition to poor long-term monitoring, a major barrier to establishing accurate prevalence rates is lack of diagnostic certainty regarding the minimally conscious or vegetative state. However, in order to develop better diagnostic tactics, philosophers and researchers must better understand what drives conscious awareness.

1.2 Unravelling Consciousness

Grasping the nature of consciousness is one of the most daunting and yet vital tasks remaining in biological science (Bor, 2016). At a very basic, behavioural level, there is a distinction between consciousness ‘level’ (i.e. wakefulness) and consciousness ‘content’ (i.e. extent of awareness) (Giacino, Fins, Laureys & Schiff, 2014). Figure 1 (Laureys, 2005) illustrates the normal physiological states contrasted with pharmacological or pathological states of altered consciousness. Figure 2 (Laureys, Owen & Schiff, 2004) illustrates the possible pathways from acute brain injury and coma to the various outcomes. Table 1 (Monti, Laureys & Owen, 2010) also shows the sleep/wake, awareness, and motor characteristics of coma, UWS, MCS and locked-in syndrome (LIS). Figure 3 (Schiff, 2015) illustrates the DoC conditions highlighting zones of potential cognitive motor dissociation. Heine, Laureys & Schnakers (2016) explain that *wakefulness* refers to level of arousal whereas *awareness* is related to subjective experiences and is sub-divided into internal and external sub-types. Chalmers (1995) describes the ‘easy’ and ‘hard’ questions of consciousness. He asserts that it is relatively easy to explore how sensory stimulation leads to perceptions and awareness of the environment asserting that sensory awareness can be explained by computational or neural mechanisms. Conversely, Chalmers argues that the harder question to address is how a percept is actually experienced in a rich and personal way. That is, the subjective element of consciousness.

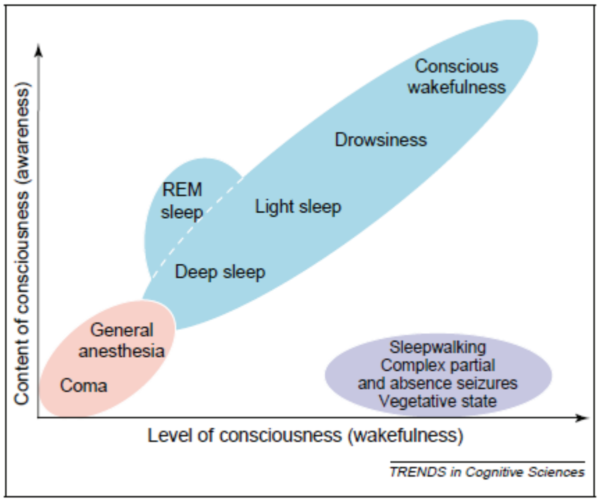


Figure 1: Two Major Components of Consciousness (Wakefulness & Awareness)

Illustration from Laureys, 2005 (p. 556) reprinted with permission showing normal physicological states (blue) contrasted with pathological or pharmacologically induced states (purple and pink respectively). The two majoir components of consciousness are shown on the x axis (wakefulness) and y axis (awareness).

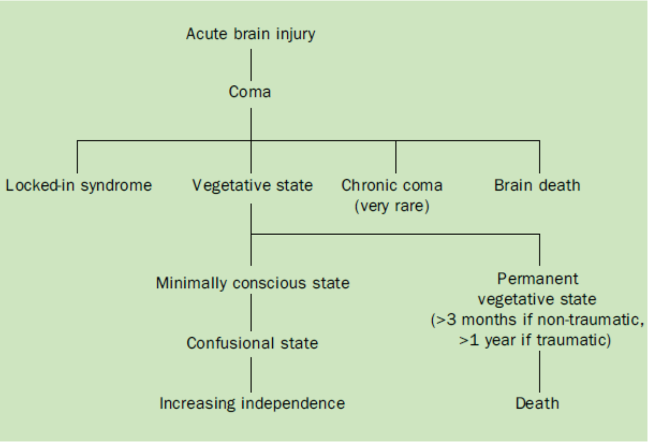


Figure 2: Flowchart of Cerebral Insult and Coma – Possible Pathways

Illustration from Laureys, Owen & Schiff, 2004 (p.537) re-printed with permission. Flowchart of cerebral insult and coma and possible pathways of progression.

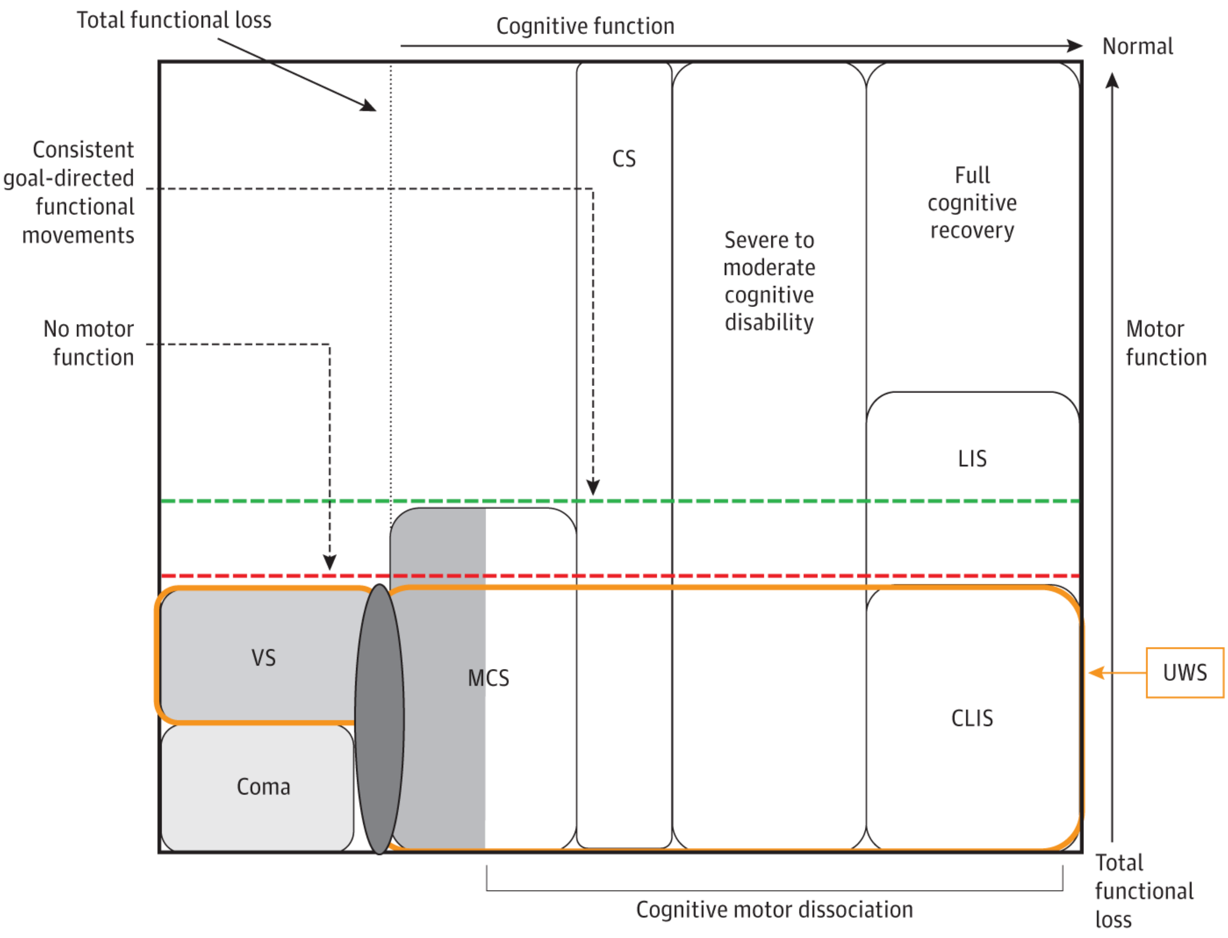
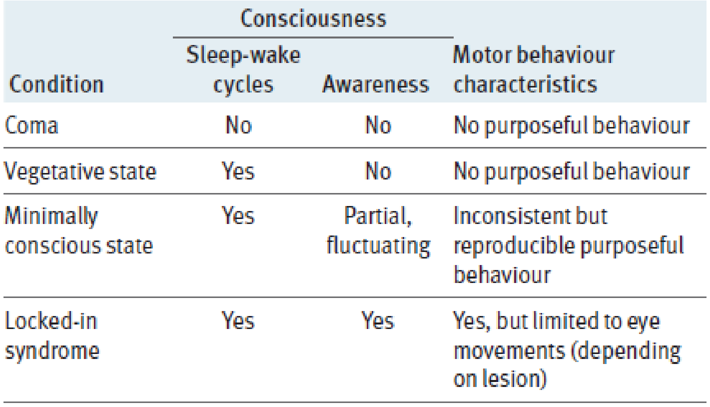


Figure 3: Cognitive & Motor Function in Clinical Disorders of Consciousness

Abbreviations: VS Vegetative State*; UWS* Unresponsive Wakeful State*, MCS* Minimally Conscious State*; CS* Conscious State*; LIS* Locked-In Syndrome*; CLIS* Complete Locked-In Syndrome

Illustration from Schiff (2015, p.1414) re-printed with permission. Clinical disorders of consciousness are represented on two axes comparing the degree of impaired cognitive function (x-axis) with the degree of preserved motor function (y-axis). Cognitive motor dissociation can occur in MCS, CS, LIS and CLIS.

Table 1: Sleep, Awareness and Motor Behaviours in DoC and LIS



Condition	Consciousness		Motor behaviour characteristics
	Sleep-wake cycles	Awareness	
Coma	No	No	No purposeful behaviour
Vegetative state	Yes	No	No purposeful behaviour
Minimally conscious state	Yes	Partial, fluctuating	Inconsistent but reproducible purposeful behaviour
Locked-in syndrome	Yes	Yes	Yes, but limited to eye movements (depending on lesion)

Table from Monti, Laureys, & Owen, (2010, p.293) re-printed with permission illustrating sleep, awareness and motor behaviours of DoC and LIS.

Although conscious cognition is associated with widespread cortical activity (Baars, 2005), there are subcortical and cortical “hot zones” in the brain. Blumenfeld explains that multiple structures and networks support conscious perception including medial frontal and parietal, anterior and posterior cingulate cortices, lateral and orbital frontal, anterior insula, and lateral temporal-parietal association cortex. Higher-order association cortices interact with sub-cortical structures involved in arousal such as the midbrain and upper pons, thalamus, hypothalamus and the basal forebrain (Blumenfeld, 2016). Functional neuroimaging studies have demonstrated that there are distinct, negatively correlated neural networks that mediate environmental versus self-awareness. Extrinsic awareness activated lateral fronto-parietal cortices whereas the intrinsic awareness activated the precuneus/posterior cingulate, anterior cingulate/ mesiofrontal cortices, and parahippocampal areas (Vanhaudenhuyse et al., 2011). It is postulated that DoC can arise from partially disconnected corticothalamic networks which regulate elements of conscious awareness such as arousal, attention, and initiation (Giacino et al., 2014).

Bor (2016) asserts that the two most widely accepted models of consciousness are the global neuronal workspace (GNW) theory and integrated information theory (IIT). Both theories emphasize network-based global integration of information and the ability of the networks to represent several functional states. The computerized GNW model (Dehaene & Changeux, 2011) is derived from the psychological/philosophical global workspace

(GW) theory (Baars, 1988; Baars, 2005) which asserts that attention is the gateway to conscious perception and works in concert with working memory. The GW theory stresses the importance of the prefrontal parietal network (PPN) including thalamocortical and corticocortical connectivity networks in facilitating consciousness. Domain-specific local processing is the source of conscious content but this content is only accessible when integrated in the global workspace, largely driven by the prefrontal parietal network (PPN). Approximately 300 ms is needed to ignite conscious activity in the PPN. This activity occurs in an all-or-none fashion and is synchronized in the high gamma band (Dehaene & Changeux, 2011).

The ITT (Tononi, 2004) is mathematically formalized and emphasizes the capacity of a system to integrate information from a variety of sources. In the case of consciousness, discrete neural correlates that are uninterpretable if considered independently, are selectively integrated into specific, but varied conscious experiences. In essence, the whole is greater than the sum of the parts and a distributed set of sources can work collectively to solve problems that individual components could not solve alone. According to this theory, it is impossible to break down the whole into component parts once these parts have been integrated. Toroni explains that due to the number of connections in the brain, the state of each element is causally dependent on that of the other elements and disconnecting the elements disrupts consciousness. Gordon and colleagues (2018) identified three separate connector hubs that interconnect discrete lower-level sensory and default mode networks to integrate information and thus enable top-down control of separate processing streams. Using fMRI, the group demonstrated that different cognitive and motor symptoms occurred when each specific hub (control-processing, cross-control, and control default hubs) was selectively damaged. Figure 4 depicts the locations of the hubs on the cortex. For instance, the hub coined the "control-default connector", showed a high level of connectedness between the fronto-parietal, default mode, and contextual association networks and was localized to the "dorsal angular gyrus, superior and inferior frontal gyrus, retrosplenial cortex, precuneus, and ventromedial prefrontal cortex" (p. 1688).

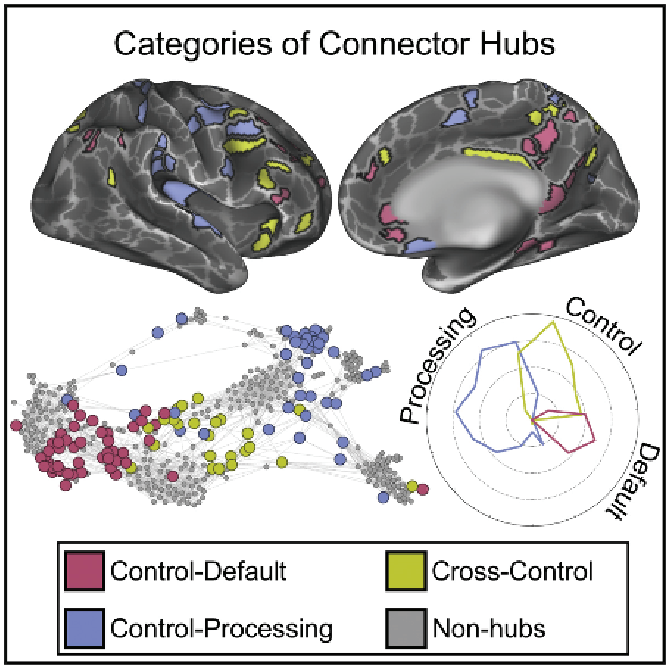


Figure 4: Three Distinct Neural Connector Hubs

Illustration from Gordon et al., (2018, p.1687) re-printed with permission showing three distinct connector hubs with control-processing, cross-control, and control-default elements.

With the idea of structural inter-dependency in mind, the Mesocircuit Model (Schiff, 2010) is an alternative, physiologically grounded model that considers anatomical connections. In all severe brain injuries, the anterior forebrain function is downregulated due to disconnection or neural cell death. Schiff argues that damage to the central thalamus reduces thalamocortical and thalamostriatal outflow. This in turn reduces afferent drive to neurons of the striatum. If the striatum is not activated, there is a loss of active inhibition from the striatum which allows GABAergic neurons of the globus pallidus interna to repeatedly fire, further inhibiting the system. This model explains the overall dampening of the consciousness system, even if many subcomponents are still functional. Figure 5 illustrates the Schiff Mesocircuit Model (embellished by Giacino, Fins, Laureys & Schiff, 2014) and Figure 6 shows Schiff's original cartoon that shows how interventions such as deep brain stimulation and medications such as zolpidem impact the mesocircuit and may alter consciousness.

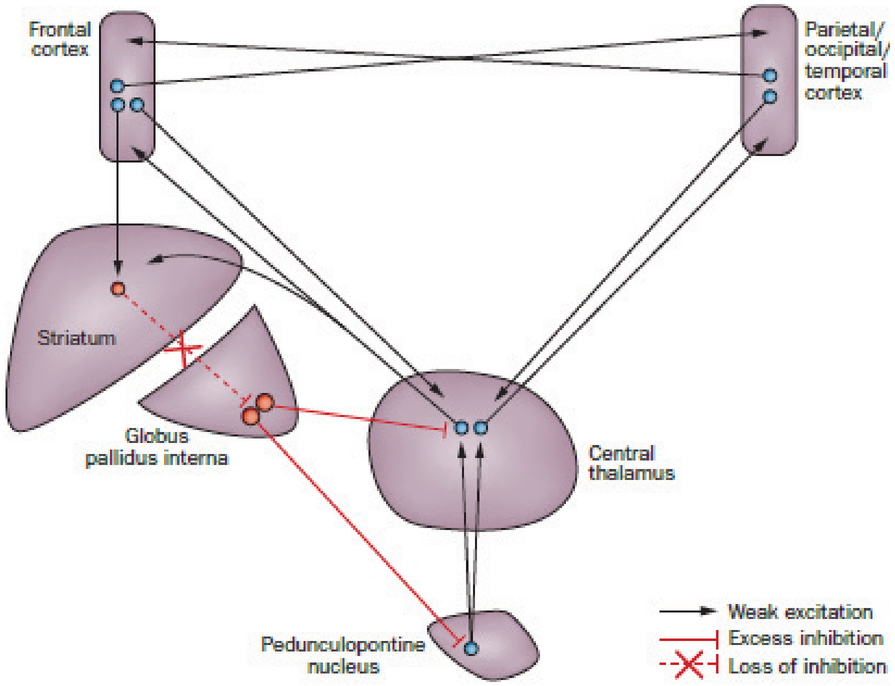
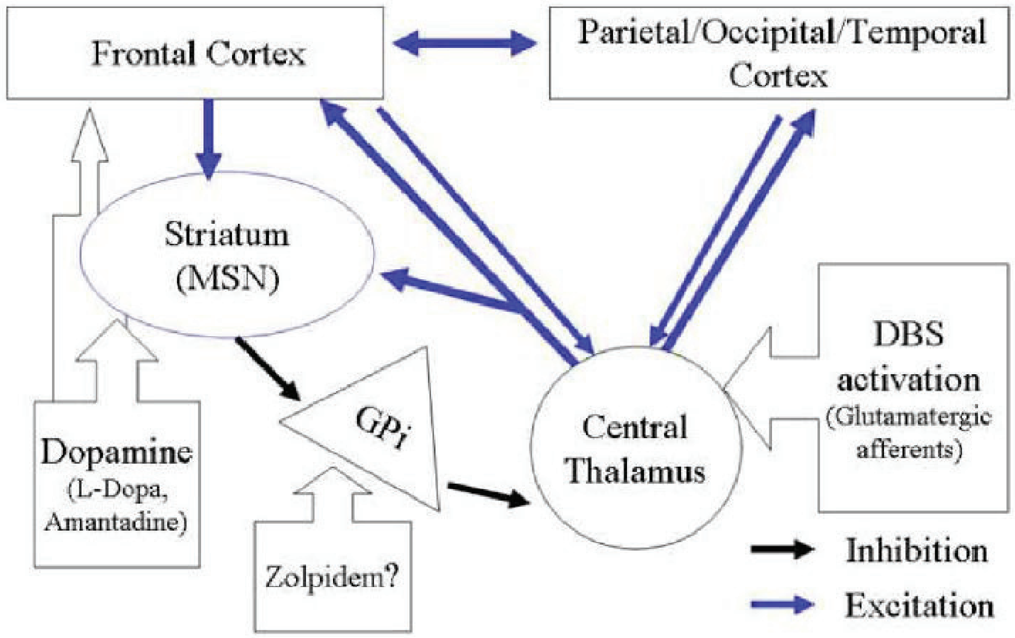


Figure 5: The Mesocircuit Model.

The Mesocircuit Model proposed by Giacino et al. (2014, p. 4) re-printed with permission which describes the effects of down-regulation of the anterior forebrain after severe brain injuries. Loss of input from the thalamus reduces input to the striatum which then fails to fire. Loss of active inhibition from the striatum permits tonic firing of globus pallidus interna which excessively inhibits thalamic firing and possibly projection neurons to the pedunculopontine nucleus.



Abbreviations: GPi Globus pallidus interna*; MSN* medium spiny neurons

Figure 6: Three Distinct Neural Connector Hubs

Illustration from Schiff (2010, p.15) re-printed with permission describing the vulnerability of the anterior forebrain (including the frontal/prefrontal cortical-striatopallidal thalamocortical loop systems) following multi-focal brain injuries that produce widespread deafferentation or neuronal cell loss and the possible interventions that restore functions in some patients.

1.3 Compromised Consciousness: Taxonomy

Disorders of consciousness exist on a continuum (Giacino et al., 2014; Laureys, 2004). Patients who survive may remain in coma, awaken but remain unresponsive to environmental stimuli, evolve to a minimally conscious state where there is some degree of interaction with the environment, or regain full conscious awareness. In an unresponsive wakeful state, also known as VS, patients demonstrate sleep-wake cycles but show no observable voluntary response to external stimulation. The 2003 United Kingdom working group for the Royal College of Physicians has suggested referring to an unresponsive state that persists 4 or more weeks as ‘persistent’ and that the term ‘permanent’ be reserved for wakeful unresponsiveness that persists at least 12 months for traumatic brain injury and 6 months for other causes before it is deemed permanent (Bates, 2005). Given the occurrence, albeit rare, of late recovery from unresponsive states there is an increasing hesitancy to refer to conditions as “permanent”. Unlike unresponsive patients, people in MCS demonstrate inconsistent but observable non-reflexive behaviour. This condition is subcategorized into MCS– and MCS+ based on the degree of responsiveness to commands. Those in MCS+ inconsistently respond to commands, whereas patients in MCS– show some responsiveness but at lower levels (e.g. visual tracking). Emergence from MCS (EMCS) occurs when patients recover functional communication and/or functional object use (Bruno, Vanhaudenhuyse, Thibaut, Moonen & Laureys, 2011). Recently, Naccache (2017) recommended referring to MCS as “cortically mediated state” (CMS) to more accurately reflect the clinical presentation and minimize confusion when communicating to families. To further compound difficulty with assessing levels of consciousness, some patients are aware and perceive normally but are ‘locked in’ and unable to demonstrate their awareness to observers. The condition was first described by Plum and Posner (1982). Lanska (2004) specifies that patients who are locked-in have injuries localized to the brainstem, typically the ventral pons. Bauer, Gerstenbrand, & Rumpl (1979) describe three types of LIS: classic, incomplete and complete/total LIS. In the classic form, patients have quadriplegia and anarthria but are fully conscious and capable of vertical eye movements and blinking as some oculmotor function is preserved depending on lesion level. In an incomplete state, the patient may have the ability to make some voluntary motor movements (e.g. head or finger switch access). In complete or total locked in syndrome, patients have no movements even in the eyes or eyelids and they are frequently misdiagnosed as unresponsive despite preserved consciousness. The case of Jean-Dominique Bauby (1952-1997) helped the general public understand the locked-in condition. Following a severe brainstem stroke, Bauby detailed his locked-in experience by dictating a book, *The Diving Bell and the Butterfly* (Bauby, 1997), letter by letter by blinking. He criticized the insensitive treatment he tolerated at the hands of some healthcare staff who were unaware of his level of awareness, thus reinforcing the need for more appropriate communication at the bedside.

1.4 Evaluating Consciousness Based on Behaviour

Medical personnel typically rely on standardized behavioural evaluations to guide the diagnostic and monitoring process. The Glasgow Coma Scale-Revised (GCS-R) (Teasdale & Jennett, 1974) was introduced over 40 years ago and is still a commonly used tool despite reliability concerns that stem from lack of standardization (Reith et al., 2016). The scale is intended to serve as a rapidly administrable, reproducible measure to gauge the severity of brain injuries and enable detection of change, especially in acute care settings. On the GCS-R, examiners rate eye, motor, and verbal responses to assess the level of consciousness on a 15-point scale with total scores ranging from 3 to 15. The score is determined by taking the best response in each category and summing the sub-scale scores for a total value. A score of 3-8 describes severe head injury, 9-12 indicates a moderate injury, and 13-15 constitutes a minor head injury (Rimel, Giordani, Barth, & Jane, 1982).

Cruse and colleagues (2012) assert that many patients in the vegetative state are misdiagnosed, despite rigorous clinical assessment. Childs, Mercer & Childs (1993) and Andrews, Murphy, Munday, & Littlewood (1996) detected misdiagnosis at 36% and 43% respectively. In the latter study, after detection of some degree of awareness, nearly all of the patients who were misdiagnosed as vegetative were able to communicate their preference in quality of life issues. In fact, Gill-Thwaites (2006) highlights that in the aforementioned study by Andrews, 70% of the misdiagnosed patients could spell messages and 90% could make choices.

Schnakers and colleagues (2009) prospectively followed 103 patients with mixed etiology and compared the clinical diagnosis (vegetative state, minimally conscious state, or uncertain diagnosis) of medical personnel with that of research staff who used the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004) to inform their diagnosis. Of the 44 patients deemed unresponsive by medical personnel; 41% were minimally conscious. The rate of vegetative state misdiagnosis was most pronounced for the chronic versus acute cases (48% versus 27%). Further, 89% (16/18) of the patients categorized by medical personnel as “uncertain diagnosis” were minimally conscious and

10% (4/41) patients who were categorized as minimally conscious met the criteria for emergence from minimally conscious.

The fact that the rate of misdiagnosis remained essentially unchanged over a 15-year span has reignited the discussion regarding the importance of differential diagnosis. The problem was further elucidated by Monti et al. (2010) who challenged 54 patients with DoC to complete mental-imagery tasks during magnetic resonance imaging (MRI) and found 5 (almost 10%) were able to modulate their blood-oxygenation-level dependent (BOLD) responses on a voluntary basis to command. Cruse and colleagues (2011) also demonstrated that despite being behaviourally unresponsive, 19% of the patients (2/5 traumatic patients and 1/11 non-traumatic patients) could repeatedly and reliably generate the target electroencephalography (EEG) response to two commands (i.e. imagine moving right hand and toes to command). This is consistent with estimates of covert awareness in studies using fMRI. Further, no relationship was established between aspects of the patients' histories (e.g. age, behavioural score, time since injury). Notably, approximately 25% of healthy controls in the Cruse study were unable to alter their EEG by imagining movement. Logically, if an error rate of 25% was observed in healthy controls, an error rate of *at least* 25% should be expected in patients as their performance may be also confounded by fluctuating arousal, sensory deficits, occult illness, pain, cognitive or language deficits, etc. Even more recently, van Erp and colleagues (2015) reviewed the prevalence of UWS in the Netherlands, finding 39% of 41 patients presumed to be unresponsive were actually at least minimally conscious. It is clear that, despite efforts to improve diagnostic accuracy at the single patient level, patients continue to be misdiagnosed in clinical settings. Figure 7 demonstrates the rate of misdiagnosis in multiple studies. Giacino and colleagues (2014) purport that misdiagnosis is precipitated by the lack of an objective gold standard for diagnosis and the resultant reliance on behaviour which is an unreliable indicator of consciousness. They summarize that some diagnostic errors can be attributed to patient-related factors such as fluctuating arousal level while other sources of error relate to environmental factors such as sedating medications. Gill-Thwaites (2006) attributes misdiagnosis to several major factors: a) definitions, b) differential diagnosis, c) the patients' medical and physical status, d) the assessor's knowledge, experience and availability for repeat assessments over time, e) involvement of the family and caregivers, and finally f) the assessment tool used to reach a diagnosis.

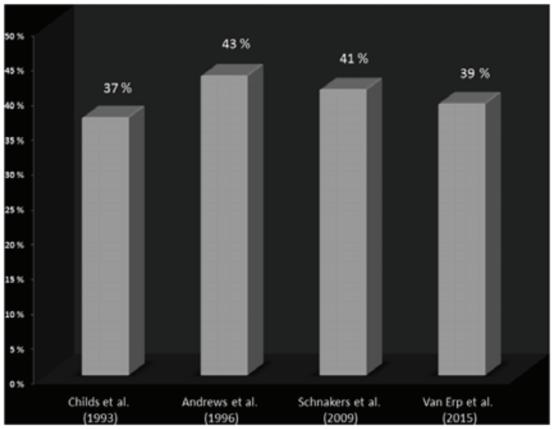


Figure 7: Percentage of Misdiagnosed Patients with Severe Brain Injury.

Illustration by Heine et al. in Monti, M.M. & Sannita G.W. (Eds.) (2016, page 28) re-printed with permission. Four studies (x-axis) demonstrating percentage of misdiagnosed patients with severe brain injury in a bar graph.

1.5 Major Factors Precipitating Misdiagnosis

1.5.1 Definitions

In the past, several terms have been used to describe alert patients who were unable to respond including apallic syndrome, akinetic mutism, post-coma unawareness, post-traumatic unawareness and persistent and permanent vegetative states (Gill-Twaites, 2006). In an attempt to standardize nomenclature and differentiate the states of disordered awareness, working groups such as the 2003 Royal College of Physicians in the United Kingdom (Bates, 2005) and others in the United States (Giacino and Kalmar, 2005) have detailed the behaviours characterizing each condition on the continuum. Despite more specific reference criteria, confusion and inaccuracies continue to arise (Gill-Thwaites, 2006) and debate continues regarding the best taxonomy.

As previously mentioned, Naccache (2017) identifies a problem with using the term MCS namely that the name includes the word “conscious” even though it is unclear whether the non-reflexive behaviours upon which the diagnosis of MCS is based actually reflect conscious awareness. Furthermore, he proposes changing the term to “Cortically Mediated State” (CMS) and suggests a new classification for DoC that combines behavioural observations with functional brain imaging to directly probe conscious processes. Similarly, Bayne, Hohwy, and Owen (2017) recommend reforming the DoC taxonomy to incorporate ways to describe covert consciousness detectable only with non-behavioural, neuro-technology assessment tactics. It is probable that definitions will continue to evolve as finer diagnostic distinctions become possible with technological advances.

1.5.2 Differential Diagnosis

Giacino, 2004 asserts that establishing an accurate diagnosis is a critical component of outcome prediction in patients with DoC. He explains that the diagnosis of MCS appears to be associated with a more favorable prognosis for recovery of function, particularly when it is diagnosed early in the course of recovery from traumatic brain injury. Katz and colleagues (2009) demonstrated that between 1-3 months post coma onset, more than 70% of patients in MCS emerged from the condition. These authors emphasize the need to differentiate the groups using repeated clinical measures as well as imaging and neurophysiologic tools. Faugeras and colleagues (2018) determined that patients diagnosed as MCS at an early stage (less than 3 months after injury), survived more often and recovered better than patients with UWS, stressing that early accurate clinical diagnosis of UWS or MCS conveys a strong prognostic value. Further, unlike patients in an UWS, approximately one third of patients in MCS improve more than one year after coma onset (Luauté et al., 2010). The recent comprehensive systematic review by Giacino and colleagues (2018) also found patients in MCS have a better prognosis than those in VS, although with low to moderate confidence in adult populations. In the systematic review and meta-analysis conducted by Kotchoubey & Pavlov (2018), 321 datasets were evaluated and of these, 13 included only MCS, 248 included only UWS, and 120 contained both groups. In this review, the authors queried whether outcome could be predicted simply by diagnosis. They found that by combining the data, MCS patients recovered consciousness significantly more frequently than UWS patients. Importantly, patients who are misdiagnosed as unresponsive have less access to rehabilitation than those who are minimally conscious (Larrivee, 2017). Given the opportunity for rehabilitation, some slow to recover patients with severe brain injury are capable of significant functional recovery months or even years post-injury (Gray & Burnham, 2000).

Despite valiant efforts to provide clear guidelines for differential diagnosis, there is a worldwide failure to use uniform protocols and as a result, assessment of patients is haphazard (Province, 2005). Liberati, Hünefeldt, and Belardinelli (2014) argue that it is vital to empirically validate the distinction between MCS and VS. However, in their review of literature of behavioural, EEG, Positron Emission Tomography (PET,) and Magnetic Resonance Imagery (MRI) measures, over half of the analyses (24 of 47) did not reveal statistically significant differences between VS and MCS. This either reflects that there is no difference to detect between the groups – which seems unlikely given patients in MCS fair better over time, or the tools used for diagnosis are, as of yet, too insensitive to detect the subtle differences between the groups. One the major challenges is that there is no existing consciousness benchmark against which to judge the efficacy of newly devised diagnostic tools.

1.5.3 Patient’s Medical and Physical Management

Physical, systemic, sensory perceptual and pharmacological barriers may compromise the patient’s ability to participate in evaluations of conscious awareness. Patients with severe brain injuries often have multiple medical problems (Giacino, Katz, & Whyte, 2013). Whyte, Ponsford, Watanabe, and Hart (2010) point out that rehabilitation must minimize medical complications and enhance the patient’s overall health and physical integrity so that natural recovery can occur (as cited in Giacino, Katz, & Whyte, 2013). Giacino indicates pre-existing conditions (e.g. diabetes), bodily injuries/conditions related to the accident or injury (e.g. liver laceration) and secondary effects of the brain injury (e.g. seizure disorder, pain, spasticity, positioning challenges, respiratory challenges, sensory-perceptual limitations, dysphagia) complicate care, slow recovery of function, and interrupt or limit rehabilitation process. Sedating medications and abnormal metabolic states can also adversely impact arousal and affect the outcome of behavioural assessments (Zasler, 2012).

1.5.4 Assessor's Knowledge, Experience & Availability for Serial Assessment

Gill-Thwaites (2006) stresses that evaluations of consciousness must be completed by competent staff who have the time and opportunity to re-assess patients over time. Examiner knowledge, competence and observational prowess play a key role in ensuring behavioural test reliability and validity, especially when a gamut of factors exist that can impact the performance of patients with complex conditions. Evaluating a patient's state of conscious awareness is challenging and requires assessment by a multidisciplinary team with specialized skills and experience in complex disorders (Andrews, 1996). Davis (1991) indicates that, given the rarity of disorders of consciousness, it is difficult for clinicians to gain experience in the field and, as a result, they may overlook or misinterpret responses. A recent international review by Reith, Brennan, Maas, & Teasdale (2016) revealed a lack of standardization in application of the GCS-R, which contributed to reduced test-retest reliability. It is logical that examiner competencies impact the accuracy of the CRS-R diagnosis as well, as a tool is only as good as the examiner(s) who employ it. Schnakers and colleagues (2006) attribute the error rate, in part, to a diagnosis being applied by non-expect teams with poor expertise in behavioural assessment. Peterson, Eapen, Himmler, Galhotra and Glazer (2019) stress the importance of serial assessments in establishing an accurate diagnosis, monitoring change, and providing prognostic information in the care of patients with DoC. Candelieri, Cortese, Dolce, Riganello, & Sannita (2011) demonstrate that even the time of day evaluations are performed may play an important role in the overall chance of observing visual tracking. They tested 22 patients (9 in UWS and 13 in MCS) six times per day and found that patients were most likely to track visual stimuli at 10:30 am and 3:00 pm and were least likely to track at a post-prandial time point (2:00 pm). In this study, 8/13 patients in MCS and 5/9 patients in UWS demonstrated visual pursuit on all testing occasions. The chance of observing visual tracking at least once per day for patients in an unresponsive wakeful state was 33% whilst the chance of observing visual tracking at least once per day in the minimally conscious state was 62%. Assessors must therefore be available to conduct in-depth and frequent assessments over time. Wannez, Heine, Thonnard, Gosseries, & Laureys (2017) suggest performing at least five behavioural assessments with the CRS-R on each patient within a short time interval (i.e. 2 weeks). Andrews (1996) identified the need for a multi-disciplinary, collaborative approach to comprehensive assessment and Shiel and Wilson (1998) emphasized that medical team familiarity with the patient improves diagnostic accuracy.

1.5.5 Involvement of Family/Caregivers in Diagnosis

The Ontario Neurotrauma Foundation has developed a Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe Brain Injury (Ontario Neurotrauma Foundation, Clinical Practice Guidelines, 2016) with a section dedicated to DoC. This resource acknowledges that families play an active role in the assessment of individuals with prolonged disorders of consciousness because individuals may respond at an earlier stage to their families/loved ones. This guideline also suggests that clinicians should work closely with family members of patients with DoC and provide education to help them differentiate reflex activity from higher-level responses. Gill-Twaites (2006) asserts that it is essential to actively involve family members and caregivers in the observational process that is the basis of behavioural assessment. Recognizing this, Gill-Twaites and Munday (1999) designed the Sensory Modality Assessment Technique (SMART) to incorporate family observations. This is necessary to ensure behaviours are not overlooked at any point during the day. This concept is reinforced by the aforementioned study by Candelieri and colleagues (2011) who demonstrated that time of day impacts the chance of observing behaviour. Being intimately familiar with the patient, family members may also have a better ability to draw the person out by introducing engaging material or by possessing the background knowledge necessary to recognize subtle behaviours characteristic of patient pre-injury. There is often assumption by medical teams that family members cannot accurately report behaviour and tend to over-estimate capacities, based on the idea that people have the tendency to “see what they want to see”. This assumption has largely been debunked when Jox et al., 2015 demonstrated that when 44 family members of DoC patients ranked their relative’s level of awareness there was 76% consensus with formal diagnostic tests. Further, when inconsistencies arose, the family members tended to under-, not over-estimate the patient’s capacities. Family, then, can be valuable assets when assessing individual patients and their level of environmental responsiveness.

1.5.6 Clinical Assessment Tools and Type of Stimuli Used to Reach a Diagnosis

The American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force (Seel et al., 2010) conducted a systematic review of behavioural assessment scales for DoC and provided "evidence-based recommendations for clinical use based on content validity, reliability, diagnostic validity, and ability to predict functional outcomes" (p.1795). Thirteen scales were reviewed for bedside evaluation of consciousness but only the CRS-R was recommended for the assessment of disorders of consciousness (with minor reservations). Table 2 is extracted from Seel and colleagues' (2010) report and depicts the clinical features (e.g. behavioural content, number of items, administration time etc.) of the 13 scales selected for in-depth evaluation. The CRS-R was shown to have excellent content validity in that it is a thorough multi-sensory tool and was the only scale to address all of the aforementioned quality criteria. The primary strength of the CRS-R is that it relies on operationally defined administration and scoring procedures and helps guide diagnosis. The primary limitation of the CRS-R, and other behaviour-based observation scales, is that sensory and motor limitations precipitate misdiagnosis in patients with perceptual challenges or cognitive motor dissociation. The group recommended that several other scales such as the SMART (Gill-Thwaites & Munday, 1999) and Wessex Head Injury Matrix (WHIM) (Shiel et al., 2000) could be used to assess DoC, but with more reservations. The Motor Behaviour Tool (MBT) (Pignat et al., 2016) has been developed to complement the CRS-R and identify subtle motor behaviours that could be used to identify residual awareness. A new version of this tool (MBT-r) (Pincherle et al., 2019) with simplified scoring has recently been developed as a bedside observation tool to detect motor behaviours. The tool was tested with 30 patients with DoC and had excellent inter-rater reliability. It also detected signs of residual awareness in 75% of the patients who were classified as comatose or in an unresponsive wakeful state by the CRS-R alone. Further, the MBT-r results were related to subsequent recovery of consciousness leading the authors to conclude that the tool may improve outcome prediction.

Table 2: Features of 13 Scales Reviewed by DoC Task Force (2010)

Abbreviation	Name of Scale	Behavioural Content	Number of Scored Items	
			Scales	Items
CNC*	Coma/Near Coma Scale	Visual, auditory, command following, threat response, olfactory, tactile, pain, vocalization	8	11
CRS-R	Coma Recovery Scale-Revised	Auditory, visual, motor, oral, communication, arousal	6	23
CLOCS	Comprehensive Levels of Consciousness Scale	Eye response, motor, posture, communication, general	7	7
DOCS	Disorders of Consciousness Scale	Auditory, visual, tactile, sensory, swallowing, olfactory	1	23
FOUR	Full Outline of Unresponsiveness Score	Eye response, motor response, respiration, brainstem reflexes	4	4
GLS	Glasgow-Liege Coma Scale	Eye, verbal, motor, brainstem reflexes	4	4
INNS	Innsbruck Coma Scale	Eye responses, auditory, pain, posture, oral	1	8
LOEW	Loewenstein Communication Scale	Mobility, respiration, visual, auditory, communication	5	25
RLS85*	Swedish Reaction Level Scale-1985	Responsiveness	1	1
SMART	Sensory Modality Assessment Technique	Auditory, vision, tactile, olfactory, gustatory, wakefulness, motor, communication	8	8
SSAM	Sensory Stimulation Assessment Mesaures	Auditory, vision, tactile, olfactory, gustatory, eye opening, motor, vocalization	5	15
WHIM	Wessex Head Injury Matrix	Basic behaviors, social/communication, attention/cognitive, orientation/memory	4	58
WNSSP	Western Neuro Sensory Stimulation Profile	Visual, tactile, olfactory, arousal/attention, auditory, expressive communication	5	32

*Higher scores reflect lower levels of consciousness for CNS and RLS85

Table abbreviated from Seel et al. (2010, p.1798) adapted with permission summarizing features of 13 DOC behavioral assessment scales evaluated by the DoC task force.

Schnakers and colleagues (2006) stress that insensitive behavioral assessment scales precipitate misdiagnosis. In the aforementioned study by Andrews et al. (1996), 65% of the misdiagnosed patients were either blind or severely visually impaired. This begs the question whether additional sensory modalities should be included in the bedside evaluation. Heine and colleagues (2016) tested the value of incorporating olfactory, gustatory and tactile modalities to CRS-R evaluation of 38 patients (15 UWS, 23 MCS) and found no improvement in diagnostic accuracy or outcome prediction with the addition of these elements. However, a recent combined fMRI and EEG reactivity study of 22 patients with chronic DoC using thermal stimulation (warm water to feet or hands) predicted improvement one-year post-testing (Li et al., 2015). Further, in a recent brain computer interface study assessing 13 patients with DoC, Wang and colleagues (2019) used three-dimensional audiovisual stimuli to supplement the object recognition evaluation component of the CRS-R. They found that six of the patients, all previously unable to behaviorally demonstrate object recognition, demonstrated significantly higher than chance level object detection in the multi-modality BCI based assessment.

Perrin, Castro, Tillmann & Luauté (2015) also specify that stimulus selection is an important factor in accurate DoC evaluation as the probability of observing a behavioral response improves when assessors consider the patient's history and personal preferences during evaluation. Self-referential stimuli such as the patient's own name (Fischer, Dailler & Morlet, 2008; Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Kempny et al., 2018; Perrin et al., 2006; Tacikowski & Nowicka, 2010) and own face (Tacikowski & Nowicka, 2010) are more likely to capture the patient's attention. As a result, using personally relevant stimuli increases the chance of observing voluntary motor responses in DoC (Laureys, Perrin and Brédart, 2007; Owen and Coleman, 2008). Sharon and colleagues (2013) found fMRI evidence of selective emotional processing in 4 patients in UWS and 13 healthy controls at the sight of familiar faces. Similarly, in both healthy controls and patients with DoC, the sound of a person's own name (SON) changes the regional cerebral blood flow in the superior temporal gyrus and in the frontal and parietal medial cortical structures (Laureys et al., 2004). Di and colleagues (2007) studied cerebral responses to patient's own name spoken by a familiar voice with fMRI in seven unresponsive and four patients in MCS. All four patients in MCS demonstrated activation in both their primary auditory cortices as well as their associative temporal areas. Interestingly, three of the patients in UWS also showed activation and two of these three patients subsequently showed improvement to MCS three months after the scan.

In general, stimuli with emotional valence activate more brain areas than neutral stimuli (Di et al., 2007). Di Stefano and associates (2012) studied 12 post-acute patients with DoC shown personally meaningful objects. Using the WHIM, they compared the motor behaviors evoked by personal versus generic objects. Familiar objects evoked a greater range of behavioral responses, supporting the idea that the emotional salience and complexity of the stimuli impact behavioral output in DoC. Sun and colleagues (2018) demonstrated that using personalized objects optimized diagnosis, demonstrating that five of 21 MCS patients assessed with non-personalized items were re-diagnosed as EMCS when shown personalized objects. Zhu and colleagues (2009) used fMRI to evaluate the cerebral responses to pictures with different valences (e.g. family pictures, highly stimulating pictures, and medium stimulating pictures) in minimally responsive patients. Similar to healthy controls, visual activation was observed for people in MCS, especially when shown pictures of family.

Studies that use the patient’s own name, own face, faces of family, and own objects provide compelling evidence for the use personalized stimuli during assessments. All of these factors have a bearing on the diagnostic accuracy and yet lack of assessment standards leads to inconsistent, inaccurate and inappropriate care (Giacino, Fins, Laureys and Schiff, 2014). Giacino and colleagues (2018) call for re-evaluation of current diagnostic practices given the growing body of research that suggests functional neuroimaging techniques may be able to detect signs of convert conscious awareness but acknowledge that no present diagnostic procedure has strong or even moderate evidence for use.

In best case scenarios, patients are assessed with a combination of behavioral scales, neurophysiological means, neuroimaging techniques, and tests of learning (Lancioni, Bosco, O’Reilly, Sigafoos, & Belardinelli, 2017). As depicted in Figure 8, Edlow (2018) proposes a tiered approach to the evaluation of consciousness including the CRS-R and neuroimaging tactics. A review by Wade (2018) suggests that the frequency of VS misdiagnosis is overstated given it is primarily based on outdated, small, and potentially biased studies which lack details and have not been replicated. He claims that, based on the available literature, covert awareness is rare. However, there is remarkable consistency among the various studies regarding the frequency of misdiagnosis. Even if Wade is correct and misdiagnosis is not as frequent as previously reported, diagnostic uncertainty continues to be very common and extremely problematic in clinical settings. There is a pressing need for clinically feasible, objective tools that detect conscious awareness in patients with cognitive motor dissociation (CMD). That is, those patients who have some degree of covert cognition without the means to demonstrate their capacities.

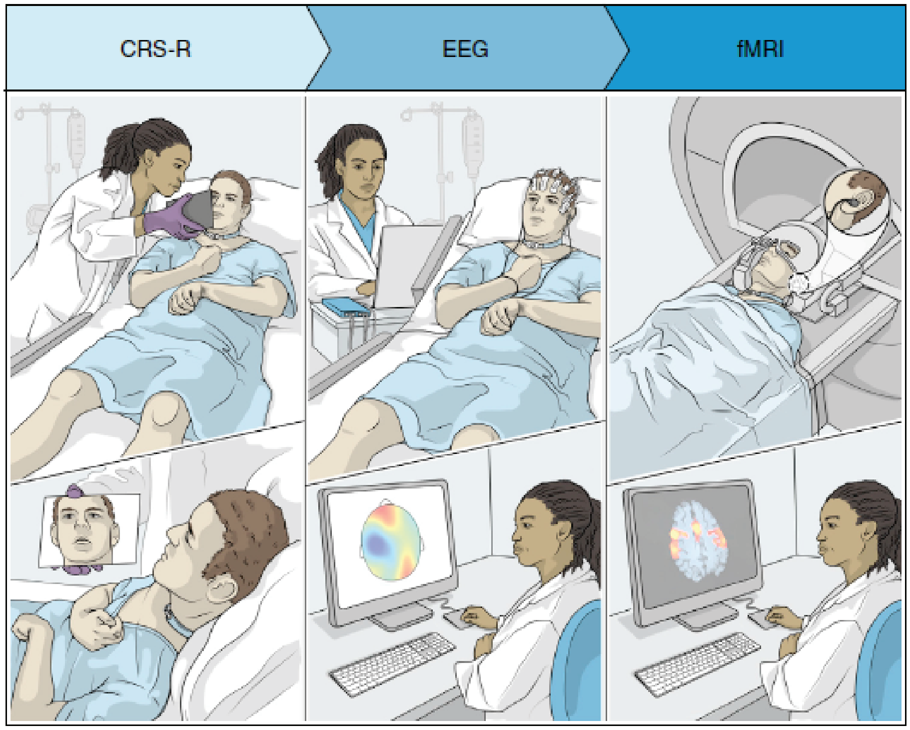


Figure 8: Tiered Approach to Assessment

Illustration from Edlow (2018, p.R1346) re-printed with permission showing tiered approach to assessment incorporating behavioral scales and neurotechnology such as EEG to speech and fMRI.

1.6 Technology Based Assessment

A comprehensive systematic review regarding disorders of consciousness clearly states that no current diagnostic assessment procedure has moderate or strong evidence for use and most protocols have insufficient evidence to support or refute their use (Giacino et al., 2018). Despite the lack of convincing evidence to date for an infallible prognostic and diagnostic tool, various tactics contribute to understanding DoC. Song, Zhang, Cui, Yang, & Jiang (2018) review brain network studies in chronic DoC concentrating on PET; functional MRI; functional near-infrared spectroscopy (fNIRS); diffusion MRI, and electrophysiology. In addition to ERPs, sleep studies, positive electromyography to command, laser evoked potentials and the perturbational complexity (PC) appear to hold some promise for advancing our understanding of DoC. These techniques will be discussed below.

1.6.1 *PET*

PET assesses brain activity and function by recording the emission of positrons from radioactively labeled molecules. PET can measure many different metabolic processes, but blood flow is typically chosen for studying DoC and Boly et al., 2008 describes a study using O-radiolabelled water PET. This study pertained to pain processing in response to bilateral electrical stimulation of the median nerve in five patients in MCS, 15 in VS and 15 healthy controls. Boly showed that in healthy controls (HC) and patients in MCS, noxious stimulation activated the thalamus, primarily somatosensory cortex (S1) and the secondary somatosensory or insular, frontoparietal and anterior cingulate cortices (i.e. pain matrix). Importantly, unlike in VS, no area was activated less activated in MCS than HC. PET studies demonstrate the importance of the association cortices (versus the primary sensory cortices) for consciousness (Song et al., 2018). Laureys, Owen, & Schiff (2004) indicate that there is no established correlation between cerebral metabolic rates of glucose or oxygen as measured by PET and patient outcome. Figure 9 contrasts the cerebral metabolism in normal consciousness, deep sleep, anaesthesia, DoC, locked in state and brain death.

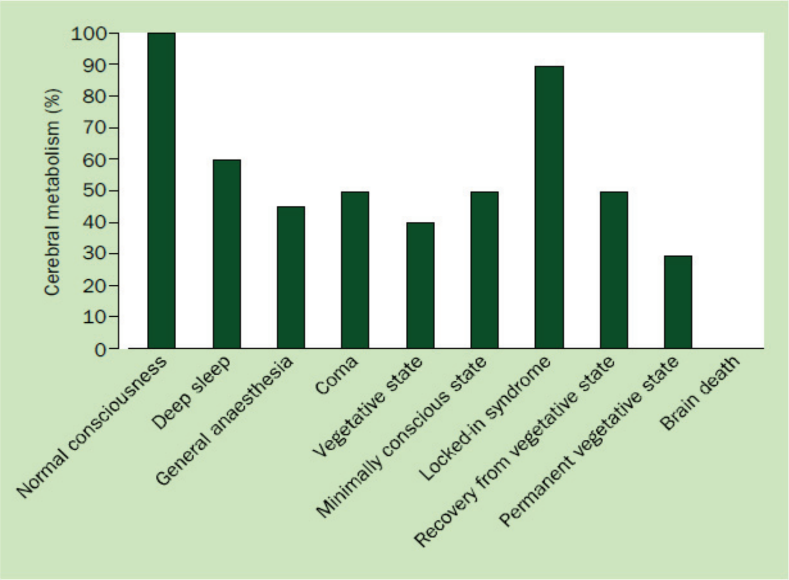


Figure 9: Percent Cerebral Metabolism and State of Consciousness

Illustration from Laureys, Owen & Schiff (2004, p.540) re-printed with permission.

1.6.2 *fMRI*

fMRI detects changes in blood flow and the primary form of fMRI uses blood-oxygen-level-dependent (BOLD) contrast (Ogawa, Lee, Kay, & Tank, 1990). Functional imaging and focal lesion patient studies have revealed a link between consciousness and the prefrontal parietal network (PPN) composed of the lateral prefrontal cortex and the posterior parietal cortex (Bor, 2016). Barring use with patients who engage in excessive movement during scanning, patients with DoC can be passively evaluated with resting-state fMRI (Song et al. 2018). In healthy people, many resting state networks, including the default mode network, is active when no explicit task is performed (Raichle & Snyder, 2007) and this may reflect internal thoughts and reflection (Buckner, Andrews, & Schacter, 2008). As demonstrated by a meta-analysis completed by Hannawi, Lindquist, Caffo, Sair, & Stevens (2015), several studies have shown reduced functional connectivity in the default mode network in patients with DoC (Vanhaudenhuyse et al., 2009; Cauda et al., 2009). Cauda and associates (2009) used fMRI to measure the resting state of 3 unresponsive wakeful patients and demonstrated that unresponsiveness is marked by decreased connectivity in several regions including the dorsolateral prefrontal cortex and anterior cingulate cortex, especially in the right hemisphere. Various other resting state networks (e.g. executive control, salience, sensory motor, etc.) are impaired in DoC and Demertzi and colleagues (2015) assert that these networks have some utility in differentiating patients in UWS from MCS. In an innovative study, Naci and colleagues (2014) used an Alfred Hitchcock movie, “Boom! You’re Dead” to evoke similar conscious experiences in healthy controls and a patient who was behaviorally unresponsive for 16 years. They found a common neural code underpinning similar conscious experiences. The evocative movie drove synchronized brain activity across frontal and parietal cortices in the healthy controls and detected strong evidence of conscious experience in the person with long-standing brain injury. In addition to these tactics, fMRI has also been used to infer awareness in conjunction with mental imagery tasks.

In the mental imagery paradigm, cortical activity is monitored while the participant is challenged to imagine motor activities. Owen and colleagues (2006) used this paradigm on a 23-year-old unresponsive woman who was five months post injury with preserved sleep-wake cycles. The woman showed increased BOLD response in the middle and superior temporal gyri in response to speech stimuli just as was observed in healthy volunteers. However, knowing that speech and sematic processing can persist in the absence of conscious awareness, the group conducted a second fMRI study and challenged the woman to a) image playing a game of tennis and b) imagine walking around her house, starting at the front door (a navigational activity) and again, observed results indistinguishable from controls which led the group to assume comprehension and command-following. A previous study (Boly et al., 2007) showed these tasks generated robust responses in healthy controls. With these remarkable findings in healthy controls and a single patient, the group conducted a larger study with 54 DoC patients (23 VS and 31 MCS) (Monti, Vanhaudenhuyse et al., 2010). Five of the 23 VS patients (22%) successfully followed commands as evidenced by fMRI activations. As establishing communication is vital, one of the subjects was selected to participate in a paradigm that challenged him to answer yes/no questions either by imagining playing tennis (“yes” response) or navigating his home (“no” response). Surprisingly, the patient answered 83% (5/6) of the questions such as, “Do you have any brothers?” correctly as indicated by the BOLD response. There is clear evidence that least some of the patients diagnosed with UWS may be responsive to external stimuli. Although successful BOLD-based responses to questions provides good evidence of masked awareness, this is not to say that the lack of response necessarily implies lack of awareness, which speaks to a lack of specificity (i.e. the ability to detect a true negative response) as other factors can impact task success.

1.6.3 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS measures infrared light through brain tissue (Villringer & Dirnagl, 1995) by comparing the absorption of oxyhemoglobin to deoxyhemoglobin in the 650-950 nm wavelength (Obrig & Villringer, 2003) with better spatial resolution than EEG (Irani, Platek, Bunce, Ruocco, & Chute, 2007) and better temporal resolution than fMRI (Agbangla, Audiffren & Albinet, 2017). fNIRS also has many practical benefits, including portability, artifact tolerance, relative affordability, and insensitivity to metal implants (Irani et al, 2007). Studies of DoC with fNIR are just starting to gain momentum. Although DoC patients have lower activity in the motor cortices during motor imagery tasks than healthy controls (N=10), no differences were detected between UWS (N=5) and MCS (N=9) using fNIRS (Kempny et al., 2016). More studies are required to determine the diagnostic or monitoring benefit of fNIRS.

1.6.4 Diffusion MRI

Diffusion-weighted imaging addresses white matter integrity and is based on molecular diffusion. Physical boundaries in the brain, especially along white matter tracts, cause higher diffusion along these tracts (anisotropic diffusion) than perpendicular to them which allows measurement of the direction of diffusion (Huisman et al., 2006). Diffusion MRI is particularly useful for diffuse axonal injury after traumatic brain injury and may be very useful in combination with other neuroimaging tactics. For instance, when used in combination with MRI spectroscopy (specifically fractional anisotropy) to detect specific metabolic compounds (specifically the N-acetyl aspartate/creatine ratio), diffusion fractional MRI was able to predict non-recovery one year post with 86% sensitivity and 97% specificity in a group of forty three patients with TBI (Tollard, et al. 2009).

1.6.5 Electrophysiology

One method for assessing real time brain activity is to record the surface electrical activity generated by the functioning brain (EEG). Quantitative EEG uses algorithms to extract complex measures of background rhythms (Forgac et al., 2014). Frequency-domain metrics of oscillatory neural activity generate electromagnetic fields at different frequency ranges or bands. The frequency bands are categorized as delta (0.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), beta (13-30 Hz) and gamma (>30 Hz) (Crivelli, Venturella, Fossati, Fiorillo, & Balconi, 2019). The EEG time series can be decomposed into a voltage by frequency spectral graph called the power spectrum.

High frequency (20-50 Hz) parietal cortex activity (Koch, Massimini, Boly, & Tononi, 2016) and frontoparietal connectivity in the alpha band is considered a potential correlate of the level of consciousness (Chennu et al., 2017). In healthy controls, Weisz, Hartmann, Müller, Lorez, & Obleser (2011) demonstrated that at rest, alpha oscillations were more pronounced than delta waves. However, alpha power decreased and delta power increased when processing stimuli. Lechinger and colleagues (2013) showed that in UWS and MCS, the alpha activity at rest was strongly decreased as compared to healthy controls. A review by Bia and colleagues (2017) also revealed that patients in an UWS demonstrated more atypical power spectrum patterns than patients in MCS. A recent multi-centre longitudinal study of 59 patients in UWS and 63 patients in MCS evaluated the prognostic capacity and diagnostic accuracy of EEG background activity and reactivity and contrasted this with clinical outcomes 6 months post injury using the CRS-R. In terms of prognostic value, only EEG background activity and reactivity significantly differed between UWS and MCS patients ($p < .001$) (Estraneo et al., 2019). This is consistent with the results of the systematic review by Kotchoubey & Pavlov (2018) showing only oscillatory EEG responses were predictive of improvement from both UWS to MCS and from UWS or MCS to EMCS. Gordon and colleagues (2018) have discovered connector hubs. The hubs in specific frontal and parietal regions appear to be important for the recovery of consciousness after brain injury (Chennu et al., 2017). Di Perri and colleagues (2016) have demonstrated that improvement of consciousness correlates with normalization of the activity within and between networks.

ERPs are non-invasive, inexpensive, and can be recorded repeatedly at bedside which makes them suitable for point of care applications. Early exogenous ERPs are induced by responses to sensory stimulation and primarily arise from integrating the physical features of stimuli. Long latency ERPs reflect more complex information processing and are therefore deemed cognitive or endogenous potentials. Long latency ERPs reflect the activity of subcortical and cortical structures, including association areas (Chatelle, Lesenfants & Noirhomme, 2017). André-Obadia and colleagues (2018) efficiently summarize the work by Sitt and colleagues (2014) stating that in chronic DoC electroencephalography, somatosensory evoked potentials, brain stem auditory evoked potentials, middle latency auditory evoked potentials, visual evoked potentials, mismatch negativity and novelty P300 to subject's own name help determine which sensory modalities are best preserved for appropriately adapting communication tools but highlights that multivariate analysis appears necessary to detect the electrophysiological signatures of consciousness. For patients who are behaviorally unresponsive, the most frequently studied ERPs are the mismatch negativity (MMN) and novelty-P3 (nP3) in response to the SON (André-Obadia et al., 2018). In cases of cognitive motor dissociation, ERPs used with brain computer interface have an important but still emerging clinical application for enabling communication. These applications will be discussed in detail in Chapter 4.

1.6.6 Polysomnography, Electromyography, Laser Evoked Potentials, and Perturbation Complexity Index

Polysomnography is considered the gold standard for sleep assessment (Berger et al., 2008; Kushida et al., 2001) and combines EEG with other measures, such as electrooculography, electromyography, electrocardiography, and measures of breath intensity to assess sleep and circadian activity (Monti, Laureys, & Owen, 2010). However, actigraphy, which measures gross motor activity with a simple sensor usually worn on the wrist, is seen as a potential alternative to the polysomnography measurement and may be more feasible and cost effective in the clinical situation. Cruse and colleagues (2013) used actigraphy to assess the circadian sleep-wake cycles in 55 patients in UWS or MCS and found that the circadian rhythms of patients in UWS significantly more impaired than those in MCS. Aricò and colleagues (2016) used 24-hour polysomnography on patients in DoC and found more preserved sleep structure (e.g. distribution of rapid eye movement/non-rapid eye movement sleep) in MCS than in UWS. Importantly, alternating periods of eyes-open/eyes closed cycles do not consistently predict preserved sleep architecture in MCS and UWS (Cologan et al., 2013). Behavioral sleep wake patterns can be observed in patients with UWS in the absence of electrophysiological patterns whereas near to normal patterns of sleep are observed in the MCS (Landsness et al., 2011). Further, this group found that sleep spindles were present more in patients who improved clinically within 6 months. Regardless of the method of assessment, assessing circadian activity is an important component of diagnosis since the absence of sleep wake cycles is an important criterion for coma. As alterations of sleep architecture are present in DoC, having sleep-wake cycles restored may be a crucial indicator of specific brain networks activity (Zieleniewska et al., 2019).

Electromyography records muscle activity and may reveal signs of subthreshold command following that are otherwise undetectable. This approach has been trialed with unresponsive and minimally conscious patients and in some cases commands such as “Please try to move your right hand” generated more EEG signal than control phrases such as “Today is a sunny day.” (Bekinschtein et al., 2008) which confirm that electromyography could help detect subthreshold voluntary movements.

Laser evoked potentials are used in the study of nociception, because laser stimulation can selectively activate pain pathways. In a study of 38 patients (Naro et al., 2015), unresponsive patients showed increased latencies and reduced amplitudes of both Að-LEP and C fibre laser evoked potentials. Since these studies may be considered necessary to determine the need for pain modulation in DoC, supplementary clues may be gained from laser evoked studies regarding the patient’s level of awareness. However, the idea of introducing painful stimuli to patients who have no ability to communicate their discomfort or voluntarily recoil poses a serious ethical quandary.

Perturbational complexity combines transcranial magnetic stimulation with high-density EEG and involves stimulating a subset of cortical neurons and measuring the effect of the perturbation on the entire thalamocortical system (Ilmoniemi et al., 1997). If perturbation is observed locally but not globally, a loss of integration can be assumed resulting in a low perturbation score. Similarly, if too many cortical regions react (i.e. loss of differentiation), the score will also be low because this creates substantial redundancy which is identified and compressed. At an individual level, Casali and colleagues (2013) demonstrated that perturbational complexity index discriminated between wakeful states, sleep, anesthesia, UWS, MCS, and LIS. Unresponsive but awake patients earned perturbation scores between 0.19-0.31, patients in MCS earned scores between 0.32-0.49 and patients in LIS demonstrated perturbational complexity index values comparable to healthy controls (0.51-0.62). This is a potentially powerful tool for differential diagnosis between UWS and MCS at the single patient level and is feasible at point of care.

1.7 False Negatives

Obtaining a false negative result, which in this instance means an erroneous negative test result in the presence of conscious awareness, is common in healthy volunteers and is even more likely in DoC patients. Patients may, for instance, have a combination of alertness, attention, sensory, memory, language or motor limitations that impair their capacity to remain vigilant, remember tasks, or follow instructions despite some preserved conscious awareness. It is vital that a negative finding is not used as unequivocal evidence of lack of consciousness or cognitive capacity (Owen & Naci, 2016). Optimally, personalized behavioral, neuroimaging, and electrophysiological measures could be combined to provide a thorough assessment, accurate diagnosis, and a more accurate prognosis in DoC while minimizing false negatives.

1.8 Emergence of Point of Care (Portable) ERP Based Systems

In 1999, Connolly, Mate-Kole, and Joyce completed a single case study demonstrating that language comprehension could be assessed without relying on verbal or behavior-based methods. Using ERPs at three midline scalp positions, they visually and aurally presented equal numbers of sentences with semantically appropriate and incongruent word endings via a computer. The patient exhibited brain responses in the form of a N400 response, indicating comprehension of the spoken sentences. This result was used to rationalize reinstatement of individualized rehabilitation with substantial subsequent gains for the patient. Thus began the era of developing tactics to circumvent overt motor or verbal behavior during the assessment of patients with disorders of consciousness.

Within the past 15-20 years, clinically oriented groups have tried to translate ERP research into clinical practice. In 2005, Hinterberger, Wilhelm, and colleagues piloted a device for the detection of cognitive activity in completely paralyzed or unresponsive patients. The small, mobile EEG based tool for detecting cognitive activity consisted of a set of auditory ERP experiments involving oddball, word matching, and semantic congruence tasks while measuring N100, P300, N400, P500, slow cortical potential shifts below one Hz, and contingent negative variation. The protocol was integrated in to the “Thought Translation Device” (TTD) software (Birbaumer et al., 1999) which uses slow cortical potentials to drive an electronic spelling device. Hinterberger tested five health controls and five patients with suspected UWS (mean age 47 years) with the DCA (Detecting Cognitive Activity) protocols. They graded participant performance based on the number of significant components and all neurotypicals exceeded significance in at least six of the eight components measured. Across the five DoC patients, zero to four components reached significance. When cumulative amplitudes were compared between the groups, healthy controls showed much higher values than the patients. The two patients who earned the best results were trialed using the TTD. The authors suggested validating the DCA approach with BCI training success but note the labor-intensive nature of this work. In a subsequent publication, Hinterberger, Birbaumer, & Flor (2005) describe using the TTD with a completely locked-in patient who, after three training sessions was able to answer yes or no questions with 62% accuracy where 50% is chance level accuracy.

In 2017, Guger and colleagues introduced the mindBEAGLE, a physiological test battery that uses auditory, vibro-tactile, and motor imaging paradigms combined with brain computer interface (BCI) technology to assess patients suspected to be locked in and enable communication in some cases. The mindBEAGLE is based on a 16 channel EEG platform with integrated hardware and software. Guger explains that it is a clinically feasible, portable system that presents the stimuli, records data, and conducts real-time data analysis. In the auditory evoked potential oddball task, patients were required to count both the frequently presented low and infrequently present high pitch tones for just over seven minutes. Two vibro-tactile tasks were conducted. The first challenged the patients to count the number of vibrations to the right and left wrists, one set of which was frequently presented and the other infrequently presented. In the second task, patients counted the frequently presented vibrations to their back or shoulder, as well as the infrequent vibrations to their left and right wrist. Each trial of four lasted 2.5 minutes. Finally, a motor imagery paradigm was employed where the patient was instructed to image left or right-hand movement for four seconds and each trial lasted nine minutes. The mindBEAGLE was trialed on five patients with DoC and three patients who were locked in. Impressively, three of the eight patients (two locked-in and one incorrectly categorized as unresponsive) communicated successfully using the mindBEAGLE system. However, across different runs and on different days, the patients showed varying abilities which reinforces the importance of serial assessment and persistence when establishing a means of communication. Despite the complexity of the mindBEAGLE tasks, 2/3 of the locked-in and 1/5 ‘UWS’ patients were able to communicate given brain-machine interface which reinforces both the need to assess patients for covert cognition and the feasibility of harnessing the power of ERPs to enable communication.

The Halifax Consciousness Scanner (HSC) was developed by D’Arcy and colleagues (2011) as a portable tool for rapid, point of care neurological evaluation after severe acquired brain injury. The intent was to supplement more routine evaluations such as brain imaging, clinical neurological evaluation, and behavior-based observation scales with data driven ERP scores linked to neural correlates of consciousness such as sensation, perception, attention, own name recognition, and semantic speech processing. This device is described in detail in Chapter 2.

1.9 Chapter 1 Summary

DoC awareness including coma, unresponsive wakeful syndrome, and minimally conscious state, have become more common with medical advances that preserve life despite severe neurological damage. Patients are often misdiagnosed as unresponsive when they may actually be minimally conscious or locked-in, partially because behavior-based rating scales cannot detect covert awareness. Harrison & Connolly (2013) summarize that the absence of evidence of conscious awareness is not always evidence of absence of conscious awareness. A conscious person may lack the ability to produce any verbal or behavioral signs of awareness. Identifying patients with covert awareness is critically important as a more favourable diagnosis may justify life preserving measures in acute care and the opportunity for rehabilitation in sub-acute and chronic settings. In response to the DoC diagnostic conundrum, functional neuroimaging and electrophysiological methods are being explored to augment clinical (heavily behavioural) scales such as the GCS-R and CRS-R. While several other types of technology are being explored, no diagnostic assessment procedure has strong, or even moderate evidence for use. Contextually or personally relevant stimuli such as familiar pictures, objects or voices appear to be more likely to evoke both behavioral and neurological responses, which has a bearing on results. Clinically oriented researchers are attempting to make consciousness testing more feasible at point of care by developing, inexpensive, portable systems with rapidly administrable, multi-sensory, personalized paradigms. One such system is the Halifax Consciousness Scanner. The auditory version has been tested on healthy controls and patients with severe brain injury. Language and literacy-free visual stimuli are also being developed.

1.10 Main Research Objectives

The purpose of this research was to further develop and evaluate the utility of Halifax Consciousness Scanner for quantifying DoC. This included developing and exploring a visual paradigm. Manuscript 1 (Chapter 3) is composed of an extensive literature review regarding the utility of evoked and event-related potentials for prognosis (awakening and early functional outcome prediction) and differential diagnosis between UWS and MCS (sub-acute and chronic phases). Manuscript 2 (Chapter 4) describes a repeated-measures, single case study. The auditory HCS was used to test a patient with persistent DoC (eight months post) after severe traumatic brain injury. Pre-testing was conducted prior to rehabilitation while the patient was awake but unresponsive (seven months post injury) and post testing was completed after seven months of intensive inpatient rehabilitation, once the patient had progressed to MCS+ demonstrating functional object use (e.g. self-feeding). Manuscript 3 (Chapter 5) details deployment and testing of the auditory HCS. The purpose of this study was to evaluate the feasibility of using the auditory HCS in sub-acute, point of care settings across the nation. An auditory oddball paradigm was used to evoke P300 responses in patients with acquired brain injury, half of whom were experiencing DoC. The P300 latencies (group level) of patients with different levels of conscious awareness (comatose, awake but unresponsive, partially responsive and fully responsive) were compared to the P300 latencies of 100 healthy controls. Analysis was also completed to examine the correlation between the P300 latencies of patients and existing clinical measures (GCS, CRS-R, and FIM – select cases). Manuscript 4 (Chapter 6) describes a visual oddball paradigm with language and literacy free stimuli (faces and places). To complete this experiment, the Raspberry Pi 3 personal computer was used in combination with the MUSE headset to deliver stimuli and record ERPs in a condensed experimental design. In this experiment, ERPs to personalized, familiar stimuli (faces and places) were compared with ERPs generated in response to unfamiliar faces and places as well as to less engaging, impersonal stimuli (i.e. X standards, 0 targets) in 15 healthy controls.

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Chapter 2: Summary of Work Related to the HCS

A knowledgeable and diverse inter-disciplinary team has recently developed an ERP based diagnostic tool for DoC called the Halifax Consciousness Scanner, (D'Arcy et al., 2011). This started by developing and coding an auditory-based paradigm, software with specialized data analysis algorithms, and robust portable hardware to permit point of care use. The system was trialed on a patient with DoC after severe traumatic brain injury before and after intensive speech-language rehabilitation (Fleck-Prediger et al., 2014 – see Chapter 4), on 100 healthy controls (Sculthorpe-Petley et al., 2015) and on 28 patients with severe brain injury (Fleck-Prediger et al., 2018 – see Chapter 5). Parvar and colleagues (2015) demonstrated that support vector machines (SVM) could help detect ERP components in individual participants with a small set of electrodes over relatively few trials. Hajra Ghosh et al. (2016) then proposed a framework for extracting specific ERPs as potential "brain vital signs" (BVS) to translate ERP data into clinical metrics. Pawlowski et al. (2018) demonstrated the viability of brain vital sign assessment and examined the difference between the auditory and visual modalities. Finally, Fleck-Prediger and colleagues worked on a project to develop language- and literacy-free visual stimuli using inexpensive, highly accessible hardware (see Chapter 6). These projects are briefly discussed in the following sections.

2.1 Towards Brain First-Aid: A Diagnostic Device for Conscious Awareness

In 2011, D'Arcy, Ghosh Hajara, Lui, Sculthorpe, & Weaver introduced the Halifax Consciousness Scanner (HCS), a portable EEG prototype device for screening conscious awareness at point of care. Tones and speech stimuli are used to evoke a range of cortically derived ERPs. The system automatically the delivers the auditory stimulation and acquires the data. It then analyzes the data, employing specialized algorithms to convert the EEG data into a numerical score for each of the five target indicators neural indicators: sensation, perception, attention, memory, and language. The raw data is manually inspected and then computer software is used to pre-process the EEG data and derive the signal averaged response. This process includes down sampling, digital filtering (bandpass 1-20 Hz and 60 Hz notch filter); segmentation (-100 to 800 ms), ocular correction, baseline correction, and signal averaging. The ERPs of particular interest include N100, mismatch negativity (MMN), P300, and N400. Based on the ERP amplitudes of signal averaged waveforms, scores are generated that consider ERP amplitudes within specified latency spans. Amplitudes are compared with component-specific baselines calculated as the average voltage of ERP onset and offset points which are generally the peaks of opposite polarity surrounding the identified ERP component.

The intent of the HCS was to develop and test a device that was non-invasive, user-friendly and rapidly administrable at point of care. Rapid administration is particularly important in clinical settings, as this patient population can be prone to rapid exhaustion. Even in healthy controls, long test sessions precipitate data quality challenges due to fluctuations in alertness and task vigilance and this problem is compounded in patients with brain injuries or disease (Neumann and Kotchoubey, 2004). Importantly, the protocol requires no overt response or effort from patients, who may not have the capacity to follow instructions.

Once the base system was developed, the system was tested on 100 health control participants. The system was then piloted on a brain injury survivor with a DoC, the results of which are described in Chapter 5 (Fleck-Prediger et al., 2015). Given the success of the pilot study, a larger cohort of patients were tested and results are described in Chapter 6 (Fleck-Prediger et al., 2018). Finally, language and literacy-free, personally relevant visual stimuli were tested on healthy controls. The results of the pilot study are detailed in Chapter 7 (Face and Places Manuscript).

2.2 Detection of Event-Related Potentials in Individual Subjects Using Support Vector Machines

Parvar and colleagues (2015) demonstrated SVMs assisted with detecting the MMN ERP component in individual participants with a small set of electrodes (Fz, Cz, or Pz) over a small number of trials (601 stimuli). The intent of that work was to determine whether SVM use would enable a condensed set up that would be more useful in clinical settings. The auditory MMN protocol was tested on 100 healthy controls with the SVM being trained to classify averaged ERP waveforms as standard versus deviant tones. Several variables such as electrode selection and temporal window size were explored. Using all electrodes, averages of all available epochs, and a temporal window of 0-900 ms post stimulus, these authors achieved 94.5% classification accuracy. The sensitivity was maintained using a narrower, sliding window to the latency range appropriate for MMN. Despite fewer required trials than typical in ERP studies, a high level of classification accuracy was achieved using SVM. Condensed testing paradigms are extremely valuable in clinical situations, as patients often do not have the endurance to withstand lengthy evaluations.

2.3 A Rapid Event Related Potential (ERP) Method for Point Of Care Evaluation of Brain Function: Development of the Halifax Consciousness Scanner

Sculthorpe-Petley and colleagues (2015) conducted the five-minute HCS test on 100 healthy controls to enable the development of a normative database focusing on N100, mismatch negativity, P300, early negative enhancement (ENE) and the N400 which reflect basic sensory, perceptual and cognitive processes. These components were evaluated at both the individual and group level using statistical and classification approaches. All components were robustly detected at the group level. The optimized SVM classification results for deviant versus standard tones, own versus other name, and semantically congruent versus incongruent sentence ending were above 90% for N100, MMN, ENE and N400 components with 99% for P300 (deviant versus standard tones). The development of a normative data base enables comparison of patient populations with healthy controls. SVM classification enables quick, highly automated data analysis.

2.4 Developing Brain Vital Signs: Initial Framework for Monitoring Brain Function Changes Over Time

Hajra and colleagues (2016) proposed a framework for extracting specific ERPs as potential “brain vital signs” (BVS) which enables the translation of complex ERP data based on N100 (sensation), P300 (basic attention) and N400 (speech processing) into accessible metrics for clinical use. BVS will be used in conjunction with the HCS to describe patient scores as explained by D’Arcy et al., (2011). A pyramidal approach was taken to translate the technical ERP nomenclature to easy to communicate brain vital signs where the sub-scores that reflect specific brain functions are derived from the mean and standard deviations. To create an elemental brain score (EBS), the linearly transformed scores are normalized to the best possible results for each amplitude and latency measure. Figure 1 shows the brain vital sign framework and Figure 2 shows the breakdown into Brain Vital Signs. The group validated the auditory protocol in 100 healthy adults ranging in age between 22-82 years, finding that specific ERPs were identifiable at the individual level 86.81-99.96% of the time. The P300 group level response was significantly more delayed in older adults and the BVS framework reflected the delays found in older adults.

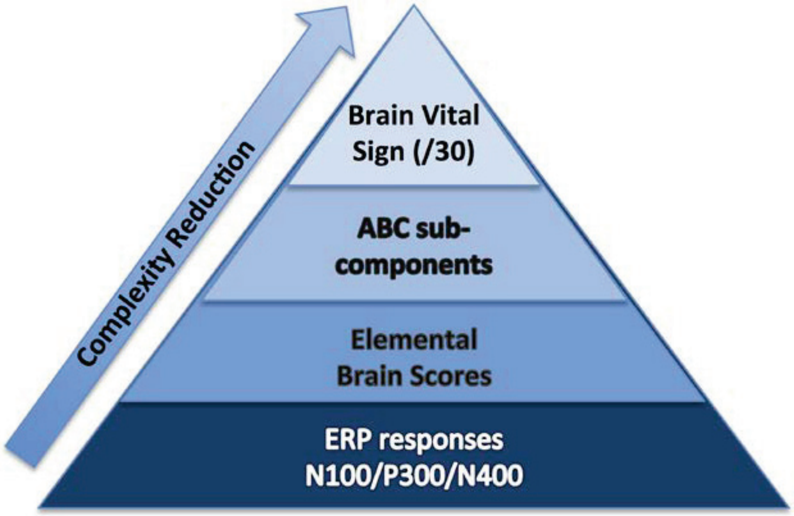

Figure 1: Brain Vital Sign Framework

Brain vital sign framework: (1) overall brain vital sign score: highest 30; (1) ABC breakdown into Auditory sensation, Basic attention, and Cognitive processing; and (2) Elemental Brain Scores linearly transformed from N100, P300 and N400 response amplitudes and latencies (3 responses*2measures = 6 scores). Figure reproduced in accordance with the Creative Commons Attribution License (CC BY).

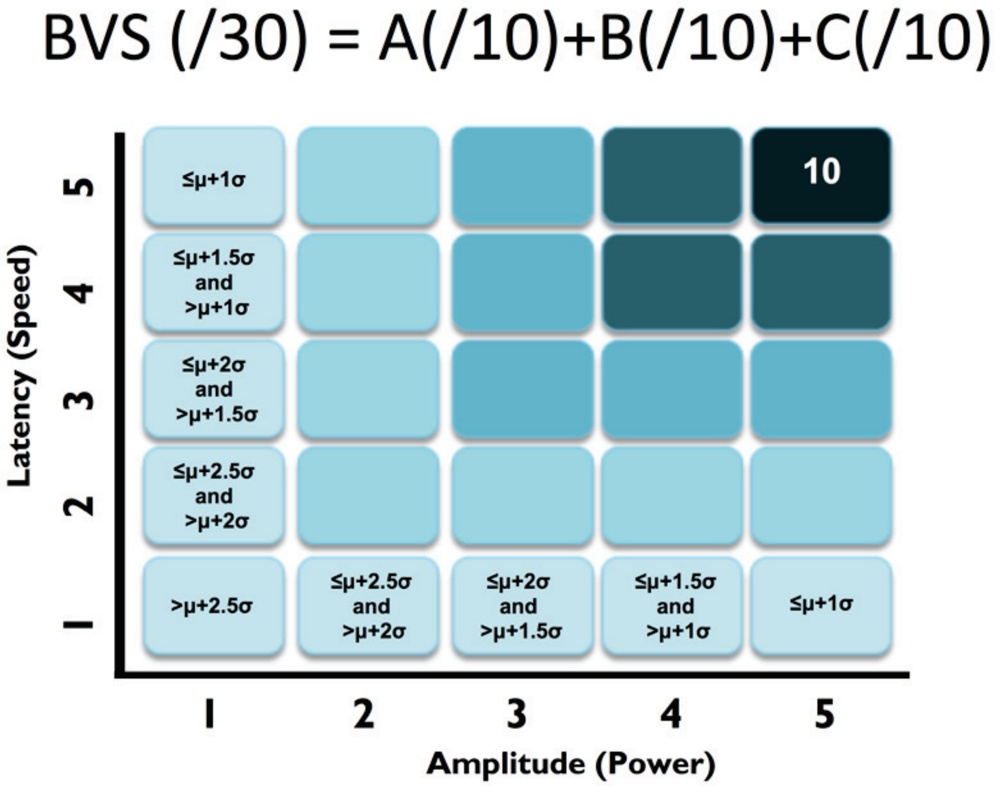

Figure 2: ABC Breakdown Demonstrating Graded Measures

ABC breakdown demonstrating graded measures. Calculation shown for BVS sub-components “A”. Similar calculations undertaken for “B” and “C”. Figure reproduced in accordance with the Creative Commons Attribution License (CC BY).

2.5 Auditory to Visual Translation (Literacy Based)

Similar to the present study, Pawlowski (2018) attempted the translation of auditory HCS sequences into a visual paradigm with the aim of demonstrating the viability of brain vital sign assessment and examining the difference between the two modalities. In Pawlowski’s study of 30 healthy adults using 64 channel EEG but focusing on Fz, Cz, and Pz electrode sites, the visual sequence used an oddball paradigm to evoke an attentional P300 response and a word pair paradigm with congruent (e.g. ‘doctor’-‘nurse’) and incongruent pairs (‘doctor’ – ‘egg’) to evoke an N400 semantic language response to incongruent pairs. The stimuli successfully evoked visual ERPs at electrode Cz. For adjusted baseline amplitudes, Pawlowski found that of the three dependent variables (N100, P300 and N400), only N400 significantly differed in amplitude across the modalities with visual stimuli (printed word pairs) inducing ERPs of lesser amplitudes than those for auditory word pairs. For latency, all three variables significantly differed between the auditory and visual modalities with shorter N100, longer P300, and shorter N400 latencies for the visual modality. The Pawlowski study relied on literacy skills for reading word pairs and did not employ personally relevant stimuli.

2.6 Multimodal Characterization of the Semantic N400 Response with a Rapid Evaluation Brain Vital Sign Framework

The Brain Vital Sign framework used with the Halifax Consciousness Scanner incorporates rapidly evoked N400 responses to interlaced semantically incongruent sentences (HCS) and word pairs. Ghosh Hajra and colleagues (2018) used magnetoencephalography (MEG) and EEG to analyze sensor level-effects and N400 brain sources in 17 healthy controls. Two data sets were removed due to poor data quality. A SVM classifier with a radial kernel was trained to distinguish between the congruent and incongruent condition waveforms using single-run, trail averaged data from Fz, Cz and Pz. Ninety percent of the data was used to train the classifier, while the remaining 10% were used for testing classification accuracy and this was repeated 10 times under 10 fold cross-validation. The classifier was therefore trained and tested on all data. The analysis was then verified using non-parametric statistics which involved randomly redistributing the congruent and incongruent class labels among all data sets, performing the same classification procedures and then repeating this process 1000 times. The N400 to incongruent (versus congruent) word pairs was significant for both MEG and EEG in the expected time range ($p<.05$). Brain activity was observed in the temporal and inferior frontal cortical regions with the expected left hemispheric asymmetry. At the individual level, the N400 effect was confirmed with high accuracy (89%), sensitivity (0.88) and specificity (0.90). This work demonstrated that the rapidly evoked N400 response evoked in less controlled settings was consistent with the N400 response evoked in traditional laboratory-based experiments, thus enabling translation of these tactics to ‘real world’ applications.

2.7 Chapter 2 Summary

In summary, D’Arcy and colleagues have conducted a series of inter-disciplinary, translational research studies. They have developed and continue to refine robust, valid and reliable paradigms, software and hardware. The focus of this group has been to develop a portable, highly automated system appropriate for use in clinical settings. The rigorous tests on healthy controls capitalize on support vector machine use to facilitate efficient data management and quantification of results. These studies have served as a springboard to research with vulnerable patients with DoC as exemplified in the work by Fleck-Prediger and colleagues (2014, 2018).

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Chapter 3: Literature Review (Manuscript 1)

Traces of consciousness: Review of the utility of evoked and long latency event related potentials in adults with pervasive disorders of consciousness after brain injury

Carolyn M. Fleck-Prediger[1,2*], Ryan D'Arcy[3,4], David Shaun Gray[1,2,5], Sandy Campbell[6], Esther Fujiwara[1,7] and Bruce D. Dick[1,8]

[1]Neuroscience and Mental Health Institute, University of Alberta, Canada; [2]Halvar Jonson Centre for Brain Injury, Canada; [3]Faculty of Applied Sciences (Engineering Science and Computing Science), Simon Fraser University, Canada, [4]NeuroTech Lab, Simon Fraser University and Fraser Health Authority, Canada, [5]Division of Physical Medicine and Rehabilitation, University of Alberta, [6]University of Alberta Libraries, University of Alberta, Canada, [7]Department of Psychiatry, University of Alberta, Canada [8]Departments of Anesthesiology & Pain Medicine, Psychiatry & Pediatrics, University of Alberta, Canada

*Correspondence address: Halvar Jonson Centre for Brain Injury Rehabilitation, Centennial Centre for Mental Health and Brain Injury, Ponoka, AB. Canada Tele: 403-783-7815; Fax: 403-783-7869; email: carolyn.fleck-prediger@ahs.ca

Chapter 3: Literature Review (Manuscript 1)

Abstract

Survivors of severe brain injury typically experience transient or persistent disorders of conscious awareness (DoC). Accurate diagnosis of the level of consciousness may allow prognostication of survival and recovery and thereby help to inform clinical decision making in intensive care. Similarly, a method of monitoring changes in the patient's consciousness status throughout recovery would help identify and direct patients who may benefit from specific treatments or rehabilitation settings. Observation and behavior-based scales, such as the Coma Recovery Scale-Revised (CRS-R) are used to quantify responsiveness in DoC but these scales do not capture all levels or types of awareness. We now understand that there is a subset of patients who are covertly aware even though they are unable to speak or move as required by behavioural assessment tools, producing a false negative assessment of their level of awareness. There is a pressing need to develop technology that detects patients with this cognitive-motor dissociation and is able to differentiate patients who are in an unresponsive wakeful state (UWS) from those in a minimally conscious state (MCS) as the latter are more likely to improve with intervention. The objective of this review is to two-fold: a) to briefly describe the prognostic value of evoked potentials and b) to critically evaluate the utility of long latency auditory and visual event related potentials (ERPs) for assisting with prognosis and differential diagnosis. A systematic search was completed, and convergent literature suggests that stimulus characteristics and paradigm demands have a bearing on ERP results. Further, evoked potentials and select ERPs have some prognostic value but long latency auditory and visual ERPs cannot be used in isolation to differentiate between UWS and MCS. However, long latency ERPs may contribute to diagnosis, especially when used in combination with other neuroimaging tactics. This review also highlights several methodological and reporting inadequacies that have been identified in the ERP literature.

Key words: Disorders of Consciousness; Electroencephalography; Evoked Potential; Long Latency or Cortically Derived ERP; Vegetative State, Unresponsive Wakeful State, Minimally Conscious State, Cognitive Motor Dissociation, Locked-In Syndrome

Chapter 3: Literature Review (Manuscript 1)

3.1 Introduction

The term ‘disorders of consciousness’ (DoC) includes coma, vegetative state or unresponsive wakeful state (Laureys et al., 2010), and minimally conscious state (Giacino, et al., 2002). Minimally conscious state has been more recently renamed the “cortically mediated state” (Naccache, 2018). Coma, primarily characterized by lack of wakefulness, is thought to stem from an organic or functional disturbance of the lower brain stem, namely the ascending reticular activating system (Young, 2009). People in an unresponsive wakeful state (UWS) or minimally conscious state (MCS) are “awake” but are either unaware (UWS) or only partially aware (MCS). These conditions are precipitated by profound damage to the neocortex, subcortical white matter and/or the major relay nuclei of the thalamus (Adams, Graham & Jennett, 2000). Recent imaging and brain functional assessment techniques have dramatically revealed that a small proportion of patients in a UWS and MCS may be in fact be covertly aware and able to process information (“conscious”) despite no outward signs of awareness (Monti, et al., 2010), a condition known as “cognitive motor dissociation” (Schiff, 2015). This ground breaking revelation highlights the need for more objective prognostic, diagnostic, monitoring and intervention tools to inform clinical decision making and guide rehabilitation.

3.2 Search Methods

A search was executed by an expert searcher/librarian (SC) on the following databases from inception to January 2018: OVID Medline, OVID EMBASE EBM Reviews (originally searched, updated in Wiley Cochrane Library January 2018), OVID PsycInfo, EBSCO-CINAHL, Proquest Dissertations and Theses Global and Web of Science using controlled vocabulary (eg: MeSH, Emtree, etc) and key words representing the concepts "disorders of consciousness" and “evoked potentials” and “brain injury”. For major databases, articles related to pediatrics, diabetes and multiple sclerosis were removed. No language or date limits were applied. This process confirmed work by Kotchoubey (2017) with search results being similar to that work.

Results were exported to RefWorks citation management system. Detailed search strategy for the primary database (Medline) is available in Appendix 1. Others are available on request from the author.

3.3 Study Screening Methods

Of the 2024 references retrieved through database searching, 1721 remained after duplicate removal. After title screening by one reviewer (CfP), 580 studies remained. After independent screening by two reviewers (CfP and BD), 69 titles remained and after full-text review 61 titles remained. Disagreements between the two reviewers were resolved through consensus for three articles. The 61 remaining studies form the literature base for this state-of-the-art review. See Figure 1 for a Prisma Reference Flow Diagram.

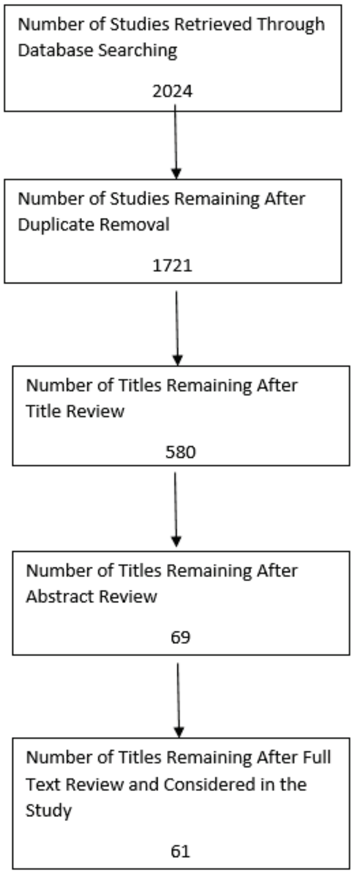


Figure 1: Prisma Reference Flow Diagram

3.4 Electroencephalography (EEG)

In the brain, billions of nerve cells produce electrical activity and these micro-currents can be detected and recorded by electrodes placed on the scalp, a fact known since the early part of the 1924 when Hans Berger recorded the first human EEG (Millet, 2002). Voltage fluctuations are either caused by an action potential or, more commonly, a postsynaptic potential (PSP) (Niedermeyer & da Silva 2005). Neurons are polarized (charged) by membrane transport proteins that create ion gradients across their membranes. The chemical nature of the neurotransmitter in the synaptic cleft determines whether the synapse is excitatory or inhibitory. If the neurotransmitter is excitatory, Na^+ or Ca^{2+} ions flow in and out (passive return current) whereas if the neurotransmitter is inhibitory, Cl^- or K^+ flow in the opposite direction (Buzsáki, et al., 2003). Jackson & Bolger (2014) explain that the dendritic generators have two poles (dipoles), negative and positive, that are separated by some distance. Depolarization results in an excitatory post-synaptic potential (EPSP), typically on the dendrites. Hyperpolarization leads to an inhibitory post-synaptic potential (IPSP), typically on the neuron cell body (see Figure 1). The combination of the EPSP and IPSP induces current within and around the neuron. Recorded voltages are the sum of the excitatory and inhibitory postsynaptic potentials from the apical dendrites of pyramidal cells located in the outer layer of the cerebral cortex close to the recording electrodes placed on the scalp. These pyramidal neurons tend to have synchronized synaptic activity because they are organized in a parallel fashion with columns perpendicular to the cortical surface which facilitates summation.

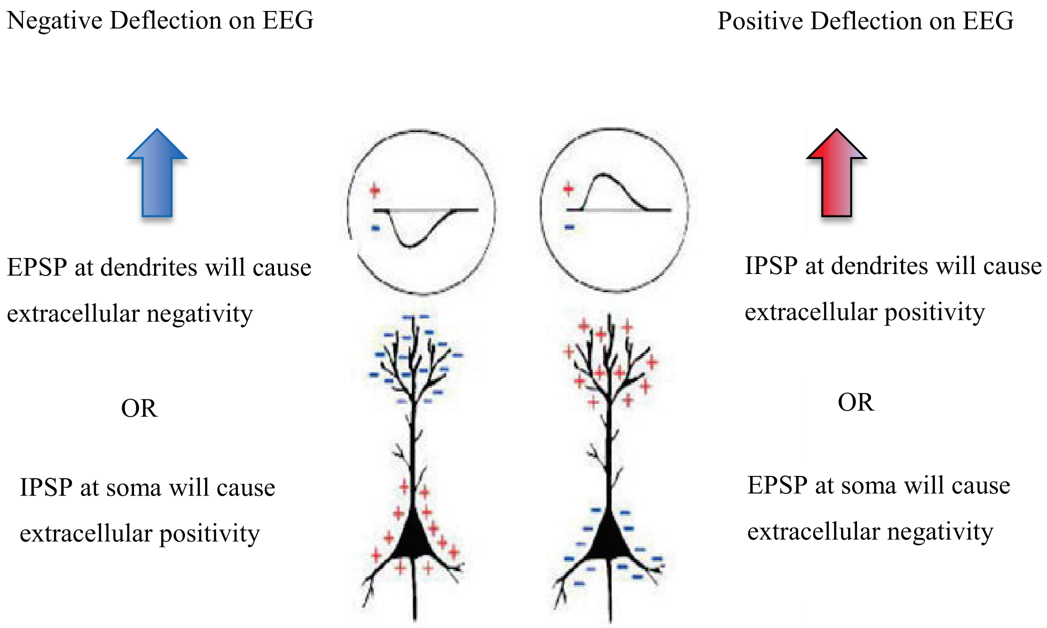


Figure 2: Cartoon of Dipole and Associated EEG Reading at Scalp

Adapted with permission from Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. (p 1063). *Psychophysiology*, *51*(11), 1061-71. Reproduced with edits (text explanation).

To be recordable at the scalp, large numbers of neurons of similar voltage fields must synchronously discharge. If the firing is synchronous, instead of cancelling each other out, the dipoles summate in larger equivalent current dipole. Therefore, an oscillating voltage recorded on the scalp reflects the activity of a large number of neurons arising from a combination of both thalamocortical and corticocortical connections (Jackson & Bolger, 2014). The spatial resolution of EEG is therefore generally poor because the EEG signal is collected from many neurons across several brain regions and the current must pass through the skull and scalp. Further, because voltage gradients fall off with the square of the distance, signals from deep sources are less likely to be detected than signals closer to the skull (Buzsáki, et al., 2003). The lack of specificity also means that the EEG signal reflects not only brain electrical activity but also other electrical signals from the whole body such as the heart or skeletal muscle contractions (Niedermeyer & da Silva, 2005).

Voltage is the potential for current to move from one place to another so there is no voltage at a single location, hence the need for active and reference electrodes (Luck, 2005, p 333). However, the choice of the reference electrode has a bearing on the timing of the ERP (Tian et al., 2018). In fact, due to the lack of a neutral (zero) point on the human body surface, any recording reference could lead to some unknown false fluctuations (Qin et al., 2010; Tian and Yao, 2013). "Average reference" is the most widely used re-referencing tactic in current practice but its value is not the ideal zero reference due to the insufficient coverage and the non-spherical shape of the human head (Yao, 2017). An alternative technique called "reference electrode standardization technique" has been proposed to mathematically re-reference the EEG recordings to infinity to get a zero reference (Yao, 2001) and several studies have verified the technique (Marzetti et al., 2007; Tian and Yao, 2013; Chella et al., 2017).

3.4.1 Brief Summary of Evoked Potentials for Sensory or Perceptual Integrity

Evoked potentials are useful diagnostic tests to identify abnormalities in the central and peripheral nervous system as they can detect demyelination (Rolak, 2010). The most commonly used modalities are visual, auditory, and somatosensory which give rise to visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SEPs) respectively (Waldman, 2009, p. 372). André-Obadia and colleagues (2018) have proposed recommendations for electroencephalography and evoked potentials in comatose patients. These authors discussed stimulation process, recording parameters, response analysis and interpretation of somatosensory evoked potentials (SSEP) to median nerve stimulation, brainstem auditory evoked potentials (BAEPs), middle latency auditory evoked potentials (MLAEPs), visual evoked potentials (VEPs), and long latency evoked potentials.

3.4.1.1 Somatosensory Evoked Potentials (SSEPs)

In critical care settings, the functional integrity of the somatosensory pathways is assessed by median nerve electrical stimulation. In coma caused by anoxia, bilaterally absent N20 components recorded one-three or more days after injury predict poor probability of awakening from coma (Wijdicks, Hijdra, Young, Bassetti, & Wiebe, 2006) however this was not true for awakening from coma resulting from traumatic brain injury. In traumatic brain injury, the absence of SSEP is also not a reliable predictor of poor prognosis (Tjepkema-Cloostermans, van Putten, & Horn, 2015). The presence of bilaterally spared SSEP, especially on day three, did however, predict functional recovery one-year post (Houlden et al., 2010).

3.4.1.2 Brainstem Auditory Evoked Potentials (BAEPs)

BAEPs, also known as Auditory Brainstem Responses reflect the neural processing of sound via the auditory nerve and protuberance (Chatelle, Lesenfants & Noirhomme, 2017). In the absence of peripheral hearing loss, absent BAEPs are associated with poorer recovery and greater chance of death (de Sousa et al., 2007).

3.4.1.3 Middle Latency Auditory Evoked Potentials (MLAEPs)

André-Obadia and colleagues (2018) explain that BAEPs must be recorded before or at the same time as MLAEPs because the latter require normal functioning of the cochlea, auditory nerve and brainstem auditory pathways. MLAEPs are also very sensitive to benzodiazepines and should not be conducted for one hour after medication administration (Morlet et al., 1997). Although few studies have evaluated the prognostic value of MLAEPs, normal potentials are associated with a greater chance of returning to consciousness. Conversely, altered MLAEPs do not necessarily imply a poor prognosis (André-Obadia et al., 2018).

3.4.1.4 Visual Evoked Potentials (VEPs)

VEPs are derived from EEG activity recorded over the occipital cortex after retinal stimulation. They can be evoked via stroboscopic flashes in low lit room or googles with red-light emitting diodes in ICU. They evaluate the integrity of the visual pathways from the retina to the visual cortex. VEPs can be considered if cervical spinal cord damage or peripheral nerve injury affects the integrity of median nerve SSEPs. Since the generators of VEPs are rostral to the midbrain, they are also the sole electrophysiological way of demonstrating cortical functioning in patients with midbrain or pontine lesions which interrupt both auditory and somatosensory pathways (André-Obadia et al, 2018).

3.5 Event Related Potentials

Evoked potentials are used for prognosis in critical care settings whereas in chronic situations, the objective is to establish a relationship between cognitive event-related potentials and consciousness (Chatelle, Lasenfants, & Noirhomme, 2017). Derived from electroencephalography, ERPs are tiny fluctuations in electrical energy extracted from continuous EEG measured on the scalp that are phase-locked to a particular event, most commonly sensory stimulation (Kotchoubey, 2017). ERPs are defined in terms of their polarity, latency, and topography. They are known to have excellent temporal resolution and therefore reflect the time course of neuronal activity patterns associated with perceptual and cognitive processes (Hillyard & Anillo-Vento, 1998). Discernable patterns emerge when many signals, time-locked to the stimulation, are averaged. Signal averaging is used to eliminate the background EEG signal and provide a measure of stimulus-related processing. The early sensory or exogenous ERP components peak within the first 100 milliseconds after stimulus presentation and depend largely on the physical parameters of the stimulus such as pitch, loudness, contrast and brightness (Licht & Hombert, 1990). Early sensory visual processing, for example, occurs within the extrastriate visual cortex and is reflected by P100 and N100 components (Olofsson, Nordin, Sequeira, & Polich, 2008).

Later cognitive or endogenous ERPs reflect stimulus evaluation and indicate higher order information processing (Sur & Sinha, 2009). ERPs have been used to measure and quantify brain responses to stimulation without requiring overt behavioural responses. This implies that ERPs could be a valuable tool for detecting masked capacities in patients with disorders conscious of awareness. A complex web of factors impact ERP results including the recording parameters, stimulus characteristics, paradigm selection and demands, and the researcher’s approach to signal processing, analysis, and interpretation. This review focuses on discussing electrophysiology research relevant to DoC targeting specific, long latency ERP components (N100, N170, Mismatch Negativity, P300, and N400) as well as the effects of stimulus characteristics (e.g., emotional valence, personal relevance) and paradigm demands (active versus passive). These ERPs have been shown to reflect fundamental cognitive processes such as perception, attention, processing, memory, and semantic abstraction (Connolly & D'Arcy, 2000; D'Arcy, Connolly, & Eskes (2000); Luck (2005); Polich (2007). Long latency ERPs reflect a more complex stage of information processing but can be adversely impacted by reduced arousal and sedating medications (André-Obadia et al, 2018). According to Gill-Thwaites, 2006), ERPs allow evaluation of stimulus permeability which may help identify patients who will respond to intervention. That is, ERPs can be used to help determine whether a specific type of sensory stimulus (i.e. auditory, visual, etc.) reaches and evokes a covert response in a patient with DoC.

3.6 Long Latency Event Related Potentials of Interest

3.6.1 N100

The auditory N100 is generated by the primary auditory cortex (Vaughan & Ritter, 1970) and is a negative deflection peaking between 90 and 200 msec after the onset of stimulus onset (Sur & Sinha, 2009). It is maximal over the frontocentral regions (Vaughan & Ritter, 1970) or vertex (Picton, Hillyard, Krausz & Galambos, 1974). The N100 reflects selective attention to basic stimulus characteristics, initial selection for later pattern recognition, and intentional discrimination processing (Vogel & Luck, 2000). The N100 is an orienting response and serves to match a new stimulus with previously experienced stimuli (Sur & Sinha, 2009).

The visual N100 is generated by the inferior occipital lobe, occipitotemporal junction (Hopf, 2002) and inferior temporal lobe (Bokura et al., 2001). The visual N100 appears to have two subcomponents manifested at the scalp, the first over the central midline at 100 ms and the second over a posterior site at 165 ms (Vogel & Luck, 2000). The response at 100 ms is only present if motor response preparation is required.

The visual N100 is larger during challenging visual discrimination tasks, because more processing is required (Luck, 1995). Features such as color, motion and shape are captured in multiple cortical areas at latencies between 100-150 ms (Hillyard & Anillo-Vento, 1998).

3.6.2 N170

The N170 occurs between 156-189 ms (Bentin, Allison, Puce, Perez, & McCarthy 1996). Faces, relative to non-faces, elicit a negative potential peaking at approximately 170 ms at lateral occipitotemporal sites particularly over the right hemisphere (Bentin et al., 1996; Rossion et al., 1999). The potentials are generated from the fusiform gyrus (Allison et al., 1999; Bentin et al., 1996; Kanwisher, McDermott, & Chun, 1997) or lateral occipitotemporal region outside the fusiform gyrus (Schweinberger, Pickering, Jentzsch, Burton, & Kaufmann, 2002). The N170 component is face-sensitive, but its specificity for faces is controversial. For example, a patient suffering from prosopagnosia did not show an N170 response to faces (Bentin, Deouell, & Soroker, 1999). However, some authors have found the N170 also occurs for highly familiar stimuli (Schendan, Ganis & Kutas, 1998) and may in reflect categorization (Rousselet, Macé, & Fabre-Thorpe, 2004) or expert recognition (Tanaka & Curran, 2001). To counter, Xu & Kanwisher (2005) used magnetoencephalography (MEG) to demonstrate what they coin a "M170" which was specific to faces and not cars, even for car experts. The conclusion was that early face processing marked by the M170 is indeed specific to faces and not simply to any objects of expertise. Rousselet found animal faces precipitated a N170 of similar amplitude to human faces in natural scenes, but with delayed peak latency.

Several factors may affect N170 manifestation. Picture inversion enhanced the N170 to human faces only but delayed the peak latency for both human and animal faces. Itier & Taylor (2004) found that the N170 was earlier and larger to faces than to seven categories of objects and that supplementary activity in the lateral temporal regions accounted for the 'specificity' of faces versus objects. Eyes alone often elicit a larger N170 than full faces (Bentin et al, 1996) and it is speculated that N170 for faces versus eyes may be elicited by different temporal neuronal populations, situated close to each other (Itier & Taylor, 2004). Itier, Alain, Sedore & McIntosh (2007) propose that the face-specific effects are mediated by the eye region and propose a neural model of face processing in which face and eye selective neurons in superior temporal sulcus respond differently to the face configuration and eyes depending on the face's context.

3.6.3 Mismatch Negativity

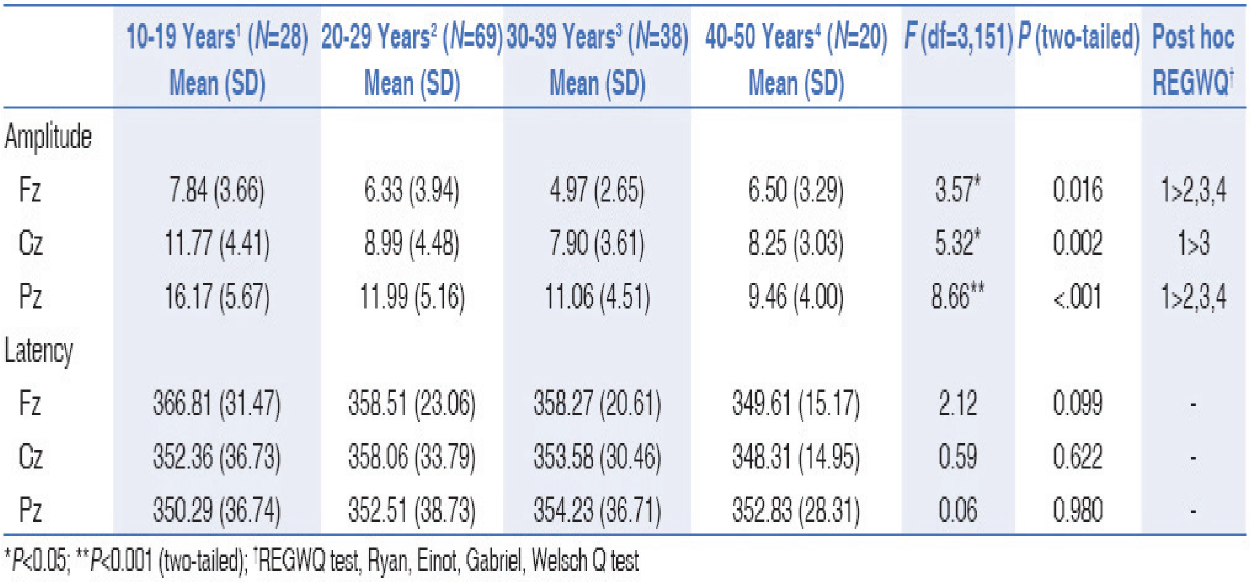
The auditory mismatch negativity (MMN) is evoked when a train of identical stimuli are presented with occasional interspersed deviant stimuli exhibiting different properties such as pitch or intensity. This negative waveform is largest at the frontal and central electrode sites (Liebenthal et al., 2003) and typically peaks between 160-220 ms. In a combined EEG-fMRI study, Liebenthal found that the right lateral aspect of the right superior temporal gyrus and right and left superior planes are important for the generation of MMN. MMN is thought to reflect an automatic process that compares incoming stimuli to a sensory memory trace of the preceding stimuli (Luck, 2005). This does not imply that MMN occurs without a degree of attention as competing tasks reduce the MMN. Rather Wickens (1984) speculates that the auditory process has its own, modality-specific attention resource. MMN is “the brain’s automatic response to changes in repetitive auditory input” (Näätänen 1990, p. 201). Within the auditory modality, MMN has been observed to changes in “tonal frequency, intensity, duration, spatial location, and many other auditory stimuli parameters” (Heslenfeld, 2003, p.41). MMN is also dependent on the number of trials, as too many deviant trials will result in habituation (McGee et al., 2001).

Heslenfeld (2003) suggested it was unclear whether MMN can be elicited in the visual modality. Kimura, Ohira, & Schröger (2010) later demonstrated with standardized low-resolution brain electromagnetic tomography that the visual MMN is distinct from the visual N100 and that visual MMN occurs with activation of non-primary visual areas and prefrontal areas. This suggests distinct neural structures for sensory and cognitive deviance detection systems in the visual system. Czigler, Balázs, & Pato (2004) for instance, conducted a MMN visual experiment to evaluate change detection by presenting infrequent color patterns within a series of frequently presented color patterns and detected the visual MMN in the 140-200 ms latency range.

3.6.4 P300

The amplitude of the auditory P300 changes over the midline electrodes (Fz, Cz, Pz), typically increasing in magnitude from the frontal to parietal electrode sites and has maximum amplitude at central/parietal recording sites (Johnson, 1993). The latency range is 250-500 ms for most adults but the range can vary depending on stimulus modality, task conditions, the participant's age, etc. (Polich, 2007). In 2018, Uvais and colleagues developed an auditory P300 ERP "normative data base for the Indian population" (p. 176) divided into four different age ranges (10-50 years) at Fz, Cz and Pz electrode sites. These data are captured in Table 1.

Table 1: Latency (ms) and amplitude (µv) of P300 in 4 age groups (10-50 years)



	10-19 Years^1 (*N*=28) Mean (SD)	20-29 Years^2 (*N*=69) Mean (SD)	30-39 Years^3 (*N*=38) Mean (SD)	40-50 Years^4 (*N*=20) Mean (SD)	*F* (df=3,151)	*P* (two-tailed)	Post hoc REGWQ†
Amplitude							
Fz	7.84 (3.66)	6.33 (3.94)	4.97 (2.65)	6.50 (3.29)	3.57*	0.016	1>2,3,4
Cz	11.77 (4.41)	8.99 (4.48)	7.90 (3.61)	8.25 (3.03)	5.32*	0.002	1>3
Pz	16.17 (5.67)	11.99 (5.16)	11.06 (4.51)	9.46 (4.00)	8.66**	<.001	1>2,3,4
Latency							
Fz	366.81 (31.47)	358.51 (23.06)	358.27 (20.61)	349.61 (15.17)	2.12	0.099	-
Cz	352.36 (36.73)	358.06 (33.79)	353.58 (30.46)	348.31 (14.95)	0.59	0.622	-
Pz	350.29 (36.74)	352.51 (38.73)	354.23 (36.71)	352.83 (28.31)	0.06	0.980	-

$^*P<0.05$; $^{**}P<0.001$ (two-tailed); †REGWQ test, Ryan, Einot, Gabriel, Welsch Q test

Table extracted from Uvais et al. (2018) with permission.

According to Shukla, Trivedi, Singh, Singh, & Chakravorty (2000) age is the most important variable affecting the latency of the P300 in neurotypicals. In 115 heathy controls, they demonstrated that the latency of P300 is positively correlated with age and for <40-year-old males and females, the amplitude of the P300 wave is negatively correlated with age. Conversely, in the aforementioned Uvais study, latency up to age 50 was not adversely impacted by age. Polich (1986) asserts that increased P300 amplitudes reflect greater attention activation as more cognitive resources are committed to the task at hand. Shorter latencies indicate superior mental performance relative to longer latencies (Sur & Sinha, 2009; Polich et al., 1986) such that P300 is considered a general measure of "cognitive efficiency" (Veiga et al., 2004). In patients with dementia, P300 latency increases systematically as cognitive function worsens (Polich et al., 1986) but the component amplitude is not directly associated with the severity of the overall condition (Polich et al., 1998). The P300 component is also thought to have two dissociable parts, the P3a and P3b. Jeon & Polich (2001) contrasted P3a and P3b responses and demonstrate that the P3a from the distractor stimulus was similar in amplitude, scalp topography, and peak latency across passive and active conditions. In contrast, the P3b from the target stimulus demonstrated a much smaller amplitude, different scalp topography, and longer latency for passive compared to active task conditions. The most typical paradigm for eliciting the P3b is the oddball paradigm wherein a target stimulus is presented infrequently among more common distracter stimuli. The ratio of target to distracter stimuli must be low in order to generate high amplitude responses (Key, 2005). The subject is instructed to respond to the infrequent or target stimulus and not to the frequently presented or standard stimulus (Sur & Sinha, 2009). A novelty P300 with short peak latency is observed across sensory modalities (Yamaguchi and Knight, 1991) in frontal/central regions when a typical string of items such as numbers is infrequently interrupted by an unusual stimulus such as a dog’s bark but the response habituates quickly (Courchesne et al., 1975). Bennington and Polich (1999) demonstrated that in healthy controls, passive listening tasks yielded P300 waveforms similar to those observed under active conditions (i.e. moving right index finger). In the visual domain however, the passive viewing task yielded much smaller amplitude P300 waveforms that were morphologically different from those generated by the active task. Veiga and colleagues (2004) used a prototypical active visual P300 task while developing a normative data base for 20-30-year-old participants. They showed 30 healthy controls a circle as the frequently presented standard and a square as the infrequently presented target and instructed the participants to press a button on a joystick in response to the target. For this age span, no age differences were detected in amplitude or latency.

3.6.5 N400

The N400 is a negative deflection that peaks around 400 ms after stimulus onset although it can extend from 250-500 ms. It is maximal over central-parietal electrode sites and is thought to reflect the process of accessing and/or updating sematic memory. That is, the binding of information from the stimulus with existing representations in short and long term memory (Federmeier & Laszlo, 2009). Kutas & Federmeier (2011) discuss how N400 can be elicited by a range of stimulus types including but not limited to text, speech, photographs of faces, and objects and actions. The N400 likely arises from multiple, distinct generators (McCarthy, Nobre, Bentin, & Spencer, 1995). Semantically incongruous but syntactically viable words at the end of sentences elicit a larger N400 response that congruous words (Kutas & Hillyard, 1980a, 1980b) and the amplitude correlates with the degree of incongruence. A N400 is not generated in response to syntactically deviant words at the end of sentences (Kutas & Hillyard, 1983). Elements of the N400 differ among modalities as demonstrated by the work of Pawlowski (2018) who found that, at Cz, the auditory N400 amplitude was smaller and later than the visual N400.

3.7 Effects of Stimulus Characteristics & Paradigm Demands:

3.7.1 Emotional Valence:

Emotion plays an important role in interpersonal interaction and emotional intelligence and is considered to be an important element of human intelligence (Ptaszynski, Araki & Pzepka, 2009). Rapid processing of affective stimuli is considered vital for emotional responsivity. A fast processing route involving the thalamus and amygdala enable the rapid perception of potentially dangerous events (LeDoux, 2000). Olofsson, Nordin, Sequeira, & Polich (2008) reviewed ERP studies spanning 40 years that used pictures which differed in valence (pleasant to unpleasant) and arousal (high to low). Schupp and colleagues (2007), for instance, used extreme stimuli such as mutilations (negative) and erotica (positive) and contrasted these high arousal conditions with neutral people (low arousal). Most of the affective ERP studies used the International Affective Picture System constructed by Lang et al., 1999 (Olofsson et al., 2008). These authors summarized that valence effects have been reported at several latency ranges, including very early components. Further, affective stimulus factors primarily modulated ERP amplitude but had little bearing on the peak latency. Sato, Kochiyam, Yoshikawa &

Matsumura (2001) demonstrated that emotional expression boosts early visual processing of the face and that both fear and happiness elicit larger amplitude responses at 270 ms (N270). Fearful faces have even been shown to be processed without directed attention (Wang et al., 2012). Balconi & Pozzoli (2003) analyzed the response of 18 neurotypicals to neutral, fearful, angry, surprised, happy, and sad faces. Emotional faces elicited a negative peak at approximately 230 ms, primarily distributed over the posterior site. The N230 amplitude increased in response to expressions of anger, fear and surprise which suggested that the ERPs were affected by arousal and the unpleasant value of the stimulus.

3.7.2 Personal Relevance:

Stimuli characterized by intrinsic psychological relevance to the perceiver, negative or positive, elicit larger P300 responses than neutral material (Johnston, Miller & Burleson, 1986). Zhu and colleagues (2009) used fMRI to demonstrate that in healthy controls (N=10), familiar and moderately-highly stimulating pictures evoked cortical activity through visual networks. They showed that patients in MCS (N=9) showed similar, but less intense activation. This serves as evidence that in some patients in MCS, enticing and familiar pictures can be used to activate the residual cognitive substrates. It is noteworthy however, that in healthy control participants, activation was stable and consistent whereas in patients in MCS, the activation was unstable and inconsistent.

In a study of 50 patients in coma, Fischer, Dailler, & Morlet (2008) demonstrated that the presence of novelty P300 response elicited by the subjects' own names (SON) was highly correlated with the likelihood of awakening. After reviewing the evidence from electrophysiological and other types of studies using own name and own face paradigms, Laureys, Perrin, & Bredart (2007) asserted that reaction to one's name is not automatic but can be involuntary. They propose that a brain's response to subject's own name (SON) "may be but is not necessarily, a sign of consciousness" (pp. 732) and in some instances may be a conditioned orienting response. In an oddball task, Gray, Ambady, Lowenthal and Deldin (2004) observed an augmented P300 response amplitude to autobiographical self-relevant targets relative to impersonal targets and standards. When comparing the P300 response to the two types of targets, the mean latency was 480 ms to impersonal targets 522 ms to personally relevant targets suggesting that self-referential processing may be a higher-order cognitive process.

Kempny and colleagues (2018) evaluated the auditory ERP response to own name versus irrelevant names in 16 patients with persistent DoC (VS/UWS and MCS) and healthy controls. Interestingly, the healthy controls generated a larger amplitude P300 response to *others'* names and a later N700 response that was left lateralized to their *own* name. For patients in DoC, 4/11 patients in MCS and 1/5 patients in VS/UWS produced a statistically significant difference in ERP amplitude response to their own name versus other peoples' names. Schnakers and colleagues (2008) demonstrated that 22 patients (eight in UWS and 14 in MCS) produced a P300 response to SON but at a latency of greater than 700 ms.

Sharon and colleagues (2013) completed an fMRI study on patients in UWS/VS exploring whether they retain the ability to selectively process external emotionally laden stimuli. Four patients in UWS and 13 healthy controls underwent the fMRI scan while viewing pictures of non-familiar faces, personally familiar faces and pictures of themselves. All patients displayed face selective brain responses with further limbic and cortical activations elicited by familiar faces. The connectivity was the strongest in the two patients who later recovered. The conclusion was that patients in UWS/VS show selective emotional processing in response to emotionally salient stimuli and internal cognitive (recognition) processes implying covert emotional awareness.

3.7.3 Active versus Passive Paradigms:

Active protocols may be more helpful in detecting potentially communicative patients because a positive response reflects both comprehension of the instruction and the ability to react to the command (André-Obadia, 2018). Schnakers and colleagues (2008) demonstrated that the P300 response in healthy controls and MCS patients was of greater amplitude when the participants were asked to count their names (active condition) than when they listened without any instruction to count (passive condition). However, no

P300 differences between active and passive conditions were observed for patients in VS/UWS. Bor (2016) comments that passive paradigms may be more clinically useful because active tasks rely on the participation of the patient. Kondziella, Friberg, Frokjaer, Fabricius, & Møller (2016) conducted a systematic review and meta-analysis addressing preserved consciousness in VS and MCS contrasting active, passive and resting state paradigms. They evaluated 37 studies including 1041 patients and found that patients in MCS were more likely than those in VS to follow commands during active paradigms (32% versus 14% respectively). However, they also showed that in passive paradigms, an even larger percentage of patients in MCS showed cortical connectivity than those in VS (55% versus 26% respectively). The authors purported that active paradigms may underestimate the degree of consciousness compared to passive paradigms. Regardless of the demands of the paradigm, the authors indicate that false negative assessments are a major limitation at the single-subject level. This is an extremely important issue for this vulnerable clinical population.

3.8 Long Latency ERPs for Prognosis and Diagnosis

3.8.1 Acute Phase:

As previously discussed, several early evoked potential measures are useful for ascertaining the integrity of the sensory systems and predicting survival and awakening from coma. Fischer and colleagues (2006) proposed a model for predicting awakening or non-awakening in post-anoxic patients based on a single clinical variable (pupillary light reactivity) in combination with MMN and SEP. In this model, for post-anoxic patients only, awakening is predicted when MMN “is present and non-awakening when MMN and pupillary light reflex are absent or cortical components of the somatosensory evoked potentials are abolished (Critical Care Medicine, 2006 p.1520-1524 as cited in Fischer, 2006, p.1520). In a large meta-analysis evaluating the power of auditory ERPs to predict awakening from coma, the presence of N100, MMN or P300 significantly predicted awakening, and MMN and P300 were better predictors than N100 (Daltrozzo, Wiloand, Mutschler, & Kotchoubey, 2007). These authors concluded that prognostic assessments of low responsive patients should include MMN and P300.

Using a mismatch negativity paradigm on 30 post-anoxic patients in coma, Tzovara and colleagues (2013) demonstrated that tracking auditory discrimination could help predict awakening in a “quantitative and automatic fashion” at the single patient level. Their research demonstrated that differences in auditory discrimination between first and second recordings predicted a patient’s likelihood of survival. Deterioration of auditory discrimination between test times was observed in all non-survivors and progression of auditory discrimination predicted survival.

Cruse (2016) summarized seven main ERP prognostic studies in VS/UWS and MCS (2005-2014) where follow-up ranged from 1.5 months to 14 years. These studies looked at MMN, N200, P3b, N350 and N400. In total, 145 patients in UWS and 100 patients in MCS were considered. Table 2 describes these results but in summary, the strongest ERP predictor for recovery of consciousness and functional outcome was the presence of MMN whereas P3b was less reliable. Importantly, presence of N400 was associated with better outcomes over the long term.

Table 2: Summary of Literature Reviewing Predictive Powers of ERPs

Authors	**ERP(s)**	**UWS (n)**	**MCS (n)**	**Time**	**Result(s):**
Kotchoubey et al. (2005)	MMN	23	20	6 m	MMN Absent: 22% Improved MMN Present: 59% Improved
Wijnen et al. (2007)	MMN	10	0	1.5-5.2 m	MMN amplitude & latency predict recovery from VS/UWS
Qin et al (2008)	MMN	6	2	3 m	SON MMN presence predicts recovery of consciousness
Cavinato et al. (2009)	P3b	34	0	1 yr	P300 presence predicts recovery of consciousness
Luaute´et al. (2010)	MMN	12	39	5 yrs	MMN not associated with favorable outcome
Steppacher et al. (2013)	N400, P3b	50	39	2-14 yrs	N400 presence predicts favorable outcome
					P3b presence does not predict outcome
Wijnen et al. (2014)	N200, P3b, N350	10	0	1.5-5.2 m	Presence and amplitude of N350 predicts outcome
Total:		145	100		

Abbreviations: UWS Vegetative state/unresponsive wakefulness syndrome, *MCS* minimally conscious state, *MMN* mismatch negativity, *m* months, *yr/yrs* year/years, & *SON* subject’s own name.

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In an important, large multi-centric, international study regarding the prognostic and diagnostic markers in DoC, Estraneo and associates (2019) collected EEG background activity and reactivity, SEP and ERP (P300) at 3 months or less and compared these objective measures with each patient's clinical outcomes at six months (n= 53 VS/MCS and 63 MCS as clinically determined by the CRS-R). At the six-month clinical follow-up, these authors found that EEG background activity and reactivity at 3 months or less significantly differed in patients who were in VS/UWS versus MCS patients (p<.001). Conversely, the presence of the N20 on SEP and P300 ERP at 3 months did not differ between the groups. However, the authors specify that "good outcome was significantly more frequent in patients with moderately abnormal to normal EEG background activity than in patients with poor EEG background organization (p=.001), in patients showing EEG reactivity (p<.001), and in patients showing P300 (p=.016)" whereas the presence of SEP did not differ between the groups. These authors concluded that multi-modal clinical and neurophysiological assessments may be useful and stressed the need for international standardization of prognostic and diagnostic procedures. Early evoked potentials and passive paradigms such as the MMN and novelty P300 to SON are appropriate for acute phase of coma but after the acute phase, more elaborate electrophysiological markers are required to assist with the delineation between VS/UWS and MCS (André -Obadia, 2018).

3.8.2 Sub-Acute Phase:

In the sub-acute phase, the focus shifts from ascertaining a prognosis for awakening to a) differentially diagnosis UWS from MCS since patients who are in MCS or who are locked in are more likely to benefit from rehabilitation and b) predict a shift in level of consciousness over time.

3.8.2.1 ERPs for Differential Diagnosis:

Hauger and colleagues (2016) conducted a systematic review (2002-2016) describing the literature pertaining to the diagnostic utility of electrophysiological recordings for detecting the presence of residual cognitive capacities in patients with disorders of consciousness after severe acquired brain injury. The authors identified 24 studies that used active ERP paradigms for differential diagnosis. They concluded that although there are not yet grounds to establish firm recommendations regarding electrophysiological diagnostic procedures in DoC, such tactics may add important supplemental information especially when covert cognition is suspected. The largest study (Sitt et al., 2014) considered 143 individuals and the smallest (Gibson et al., 2014) evaluated only four to six participants (depending on task) but the Gibson study was important because it demonstrated that multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with DoC. The systematic review revealed that inadequate sample size is a major barrier to interpretation. The authors concluded that multicentre studies across laboratories are necessary to establish adequate sensitivity and specificity and assert that paradigms must be systematically validated on healthy controls. Hauger specified that the two most challenging aspects of the systematic review were a) comparing wildly diverse studies and b) not having a consciousness benchmark against which to judge the efficacy of a tool or tactic. Hauger also found that different laboratories conducting similar experiments generated conflicting results.

Kotchoubey (2017) conducted a quanitative analysis of 61 reports on ERPs in DoC from 1989-2015. Approximately two thirds of the publications compared VS/UWS and MCS. He commented that only a few of the studies were based on sample sizes sufficient to draw reliable conclusions. However, the low statistical power was predominantly a limitation in studies which compared ERPs of MCS and UWS groups. Higher power studies have been completed regarding the prognostic value of ERPs. In addition, weaker but more reliable results (versus strong but less reliable results) were more likely to be published in top ranking journals. In the review, Kotchoubey divided the quality of the articles into three levels. The criteria used to establish the level is detailed in Table 3. Level three publications were deemed the most robust. Kotchoubey ranked the quality of the clinical diagnosis in a binary manner based on whether the CRS–R was used to establish the clinical diagnosis. He further suggested that ERP studies should contain not less than 25 participants in each clinical diagnostic category. Table 4 lists the three publications that a) met the aforementioned criteria, b) pertain to differential diagnosis, and c) employ long latency visual and/or auditory ERPs. Collectively, these three articles represent the ERPs commonly used in studies of differential diagnosis and include both active and passive paradigms. Each of these studies is described below.

Table 3: Description of Process Kotchoubey Used to Assign Level of Publication

Level:	**Criteria:**
1	"Level 1 was assigned when at least one of the following statements was true: - EP/ERP were only evaluated by means of expert rating and the blindness of the experts was not warranted; - ER/ERP were described without any quantitative analysis; - The method of analysis was not described with details sufficient to replicate this analysis, or test statistics were not reported; - The statistical results were misinterpreted, that is the analysis involved several groups (coma, VS, MCS, conscious patients, healthy controls) and revealed a significant different among the groups; however this effect was interpreted as the significant difference in a particular pair of groups (e.g. VS versus MCS), although no pairwise test was reported."
2	"Level 2 was assigned, when an analysis was correctly applied and correctly described but the dimensionality of the analysis did not correspond to the dimensionality of the data, i.e., a simple univariate technique was applied to a multivariate data set, and the appropriate correction was not performed."
3	"Level 3 was assigned when a multivariate or, at least, a joint univariate method was used for assessment of ERP components in individual patients….Level 3 was also assigned when a strict univariate method was applied to EP."

Extracted with permission from the text in Kotchoubey (2017, p. 157) and reported in table form. Level 3 publications were most robust.

These reports contain adequate sample sizes (>25/group), use the CRS-R as a clinical benchmark, pertain to differential diagnosis, and employ long latency visual and/or auditory ERPs.

Table 1: Three Level 3 Reports Reviewed by Kotchoubey (2017)

Authors:	ERPs:	UWS (n)	MCS (n)	BI	HC	Results: Black Font: Some Value Red Font: Little/No Value
Sitt et al. (2014)	N1, P2, N2, P3	75	68	24	14	MMN and P300 showed only modest differences between groups. No ERP significantly differentiated VS and MCS.
Real et al. (2015)	N100, P200, P300 and Difference P300. For P300 - Active and Passive Simple Auditory Two Tone Oddball Paradigm	29	16	0	14	All ERPs were more frequent in HC. P300 marginally higher in MCS (vs UWS/VS) P300 marginally associated with CRS-R (time 2 only)
Steppacher et al. 2013)	P3 to Sound N400 to Speech (Semantic Deviance)	53	39	0	0	P300 presence was not statistically predictive of outcome. N400 presence predicted favorable clinical outcome.

Abbreviations: ERPs, event related potentials, *UWS* Vegetative state/unresponsive wakefulness syndrome, *MCS* minimally conscious state, *BI* brain injured but conscious, *HC* healthy controls

Extracted with permission from the text in Kotchoubey (2017, p. 157) and reported in table form.

Sitt et al. (2014): Large Scale Screening of Neural Signatures of Consciousness in Patients in a Vegetative or Minimally Conscious State.

Sitt and colleagues (2014) studied 14 health controls and 167 patients with brain injury, some in DoC (74 VS, 68 MCS, and 24 patients that were brain injured but conscious). Sitt performed a systematic analysis of P100, Mismatch Negativity, Contingent Negative Variation, P3a and P3b and found event-related measures showed low sensitivity for discriminating between UWS/VS and MCS patient groups. MMN was positively correlated with the level of consciousness and discriminated UWS/VS from conscious participants and MCS from conscious participants but did not differentiate patients in UWS/VS from those in MCS. Similarly, P300 did not distinguish patients in UWS/VS from MCS.

Real et al. (2016): Information Processing in Patients in Vegetative and Minimally Conscious States

Real and colleagues (2016) used a simple auditory two tone oddball paradigm presented in passive (just listen) and active (count odd tones) conditions to see if they could differentiate between VS/UWS and MCS patients. For patients, testing was completed at two time points (T1 and T2) separated by at least one week. In both passive and active listening conditions, N100, P200 and P300 were significantly more frequent in the 14 healthy participants than in the 45 patients in VS/UWS or MCS. In the patient group however, the paradigm was not sensitive enough to differentiate patients in VS/UWS from those in MCS. Three patients differed clinically between the two time points. Of these, one transitioned from VS/UWS to MCS as ascertained by the CRS-R, with no change to the ERPs between T1 and T2. Conversely two patients changed from MCS to VS/UWS. One of these two did not show activation at either time point, and the second showed a difference P300 (i.e. difference between responses to deviant stimuli minus the responses to standard stimuli) at T1 but not T2. The P300 response, on its own, is not sensitive enough to differentiate VS/UWS from MCS patients at the single subject level.

Steppacher et al., 2013: N400 Predicts Recovery from Disorders of Consciousness

Steppacher and colleagues (2013) studied ERPs elicited by sound (P300) and speech (N400) in patients clinically diagnosed as UWS (n=53) and MCS (n= 39) less than one year post-onset. The P300 task involved listening to 1000 Hz sine tones (500 non-targets), 1500 Hz sine tones (100 targets), and 100 environmental sounds at 90 dB with the instruction to count the higher pitched tones. The expectation was that the novel environmental sound would evoke the P300 response. In the N400 task, 200 five-word sentences were presented, 100 with senseless endings and 100 that were consistent with the sentence context at 90dB with the expectation that semantic deviance would evoke a N400. With long term follow up (two to fourteen years after discharge from rehabilitation), approximately 25% of the patients regained communication capacity. Long-term recovery of communication was significantly correlated with N400, but not P300. An intact N400 response appears to have some ability to predict improvement over the long term.

3.8.2.2 Predicting a Shift in Level of Consciousness Over Time:

Kotchoubey & Pavlov (2018) conducted a systematic review and meta-analysis of the relationship between brain data and the outcome of DoC. They evaluated 47 studies of neurophysiological variables (EEG, ERP, fMRI & PET) as potential outcome predictors of DoC. Of the 47 studies analyzed, 12 (approximately 26%) involved long-latency auditory ERPs (MMN, P300, and N400). No long-latency visual evoked potential studies were included in the study. The poorest prognostic effects were shown for fMRI and the P300 ERP component. However, the authors qualify by stating that although a single neurophysiological variable such as P300 may be ineffective as an independent predictor, it may still be valuable in combination with other predictors in a multivariate approach to outcome prediction. Technology-based neurophysiological data are more able to predict the transition from UWS to MCS than the transition from UWS or MCS to unequivocal consciousness (Kotchoubey & Pavlov, 2018).

3.9 Guidelines for Evoked and Event-Related Potential Use

If the utility of long-latency ERPs is to be fully explored and translated into clinical settings, ERP methodological practices need to be more consistent. André-Obadia and colleagues (2018) proposed recommendations for recording and interpreting electroencephalography and evoked potentials in post-anoxic comatose patients. They detail the prognostic value of each test, specify administration time lines, and highlight the limitations regarding recording and interpretation. This resource discusses several evaluation strategies (EEG, somatosensory evoked potentials, brainstem auditory evoked potentials, middle latency auditory evoked potentials, visual evoked potentials, etc.). It includes guidelines for long-latency measures including MMN with passive paradigms, P300 with passive paradigm evoked by the subject's own name, and P300 with an active paradigm. André-Obadia provides a valuable evaluation flowchart detailing the critical care cascade after post-anoxic coma (see Figure 2) and a table detailing the analysis of long-latency ERPs including MMN and P300 to SON (see Table 5). Likewise, Duncan and colleagues (2009) recommend methods for using ERPs in clinical research, detailing the techniques for eliciting, recording and quantifying MMN, P300 and N400. Parameters such as stimulus features, participant factors, task demands, electrophysiological recording parameters, and quantification of ERPs are discussed in great detail.

Convergent literature appears to support using stimuli with greater emotional valence in long-latency ERP studies of DoC. This can be accomplished by personalizing the stimuli (e.g. using familiar photographs of self, family or friends, using subject’s own name, or the sound of family member’s voice) or by selecting highly stimulating, captivating stimuli. While positive responses to active paradigms permit a higher degree of certainty regarding presence of covert awareness, passive and resting state paradigms are more appropriate for patients unable to cooperate in cognitive tasks due to aphasia, sensory limitations, executive disorders etc. (Kondziella, Friberg, Forkjaer, Fabricius, & Møller, 2016).

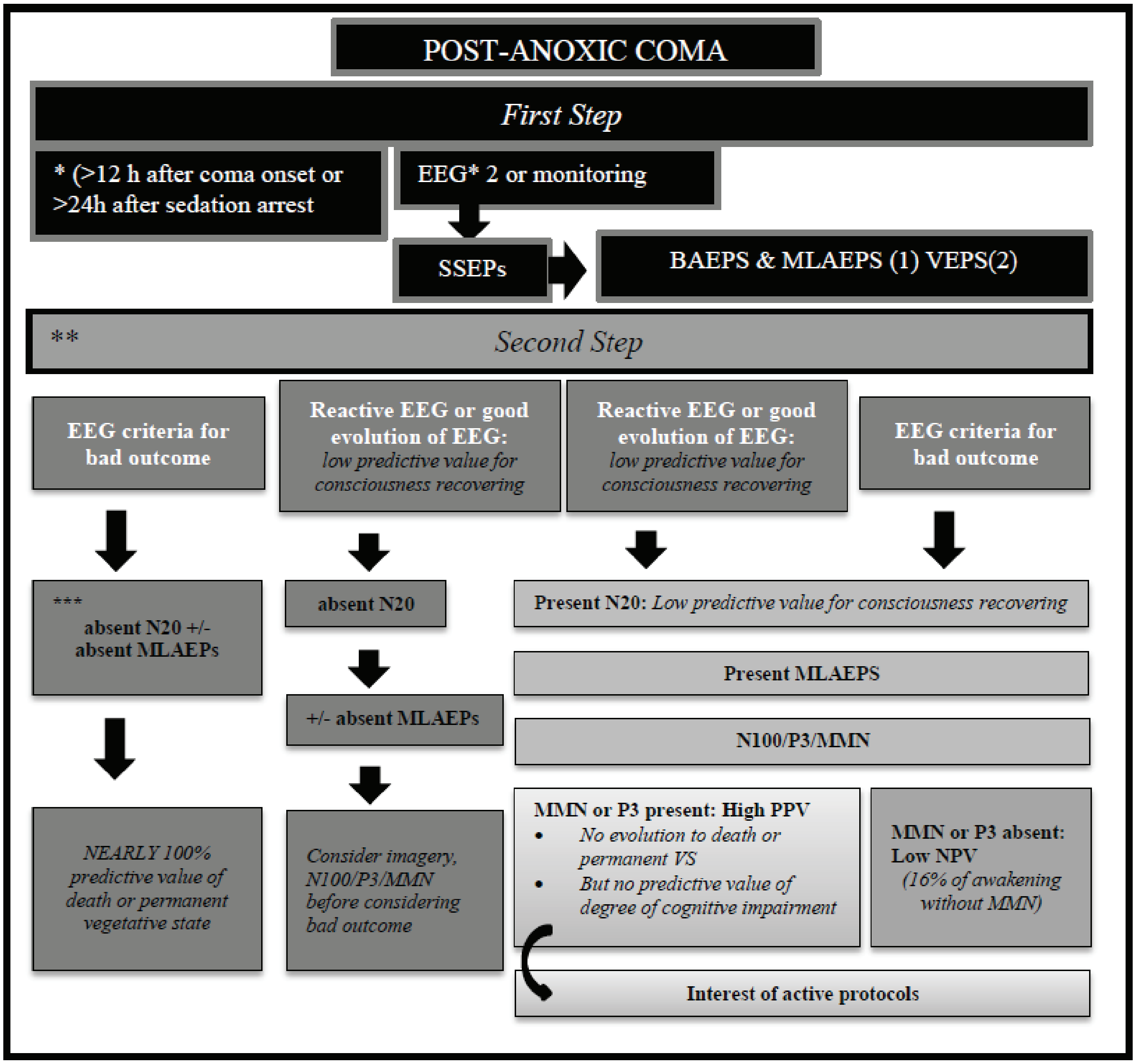

Figure 3: Post Anoxic Stroke Protocol (Comatose Patients)

*Abbreviations: EEG e*lectroencephalography, *SSEPs* somatosensory evoked potentials (N20), *BAEPS* brainstem auditory evoked potentials, *VEPs visual evoked potentials, MLAEPs* middle latency auditory evoked potentials, *MMN* mismatch negativity, PPV positive predictive value, NPV negative predictive value.

Post-anoxic coma protocol. Style (not content) edits applied to André-Obadia, N., Zyss, J., Gavaret, M., Lefaucheur, J. P., Azabou, E., Boulogne, S., ... & Naccache, L. (2018) with permission. Recommendations for the use of electroencephalography and evoked potentials in comatose patients. (p. 163). *Neurophysiologie Clinique, 48 (3),* 143-169.

Table 4: Electroencephalography & Evoked Potentials in Coma

Absence of MMN:	Presence of MMN:
N1 is recorded AND there is no difference observed by comparing averaged ERP traces for rare and frequent stimulations AND subtraction of averaged ERP traces fails to find a negativity.	N1 is recorded AND there is a local difference in the averaged ERP traces for rare and frequent stimulation AND subtraction of the averaged ERP traces reveals a negativity peaking between 100 and 250 ms, greater than the background noise, and predominant on fronto-central derivations with polarity inversion on mastoid derivation*
Absence of P3 to SON:	**Presence of P3 to SON**
No reproducible response on frontal or parietal derivations peaking after 200 ms.	Identification of a reproducible positive response, greater than the background noise, peaking after 200 ms on fronto-central derivations* (P3a), eventually followed by a second positive component on parietal derivation* (P3b)
The conditions of recordings must be good (lack of artifacts and reproducible ERP traces, absence of sedation, no status epilepticus, and spontaneous EEG traces appear suitable for analysis). *These topographical criteria are not absolute and could be absent in case of cerebral lesion, particularly for frontal topography.	

Style (not content) edits applied with permission to André-Obadia, N., Zyss, J., Gavaret, M., Lefaucheur, J. P., Azabou, E., Boulogne, S., ... & Naccache, L. (2018). Recommendations for the use of electroencephalography and evoked potentials in comatose patients. (p. 160 Neurophysiologie Clinique, 48 (3), 143-169.

3.10 Long-Latency ERPs for Brain Computer Interface

In some cases, long-latency ERPs can be harnessed for brain computer interfaces (BCI) which, when successful, enable communication and environmental access. Brain computer interfaces directly convert electrical activity at the scalp, on the cortical surface or within brain, into a computerized command (McFarland & Wolpaw, 2011). Farwell and Donchin (1988) were the first to report a P300-based spelling device. In this study, row by column scanning was used to strategically narrow down the target letter the patient intends to select. The patient focuses his/her attention on the target letter, eliciting a P300 response when that letter illuminates. The process is slow (seven to eight words per minute) but 80-90% accurate (Donchin, Spencer, & Wijesinghe, 2000). However, visually based BCI protocols are hard to implement with patients who have difficulty controlling their gaze, which led Kübler (2009) to use an auditory version. Unfortunately, users found the attentional and memory demands of auditory scanning to be too difficult to use in a practical way. Lulé and colleagues (2013) evaluated whether BCI could help detect consciousness using a four-choice auditory oddball EEG-BCI paradigm (yes, no, stop, go) on 16 healthy controls and 18 patients with disorders of consciousness. Thirteen healthy participants and one locked-in patient were able to communicate (i.e. answer yes/no questions such as "Is your name Quentin?") via BCI and one patient in MCS showed command following (i.e. concentrate on "yes" or concentrate on "no") with BCI. In a recent BCI study by Wang and colleagues (2019), 3D audiovisual stimuli were used during administration of the CRS-R to assess object recognition in 13 patients in DoC. Although none of the 13 patients demonstrated object recognition with traditional presentation/observation tactics, six of the 13 patients achieved accuracy significantly higher than chance level with the 3D BCI approach. The applications of ERPs for DoC are just starting to emerge and represent an exciting clinical direction.

3.11 Methodological Challenges

Kotchoubey (2017) specified some major concerns with the evoked potential and ERP studies he evaluated in his quantitative review. He proposed several criteria for a strong ERP study in DoC in his quantitative review. These included recommendations regarding sample size, establishing a correct clinical diagnosis, reporting all methodological details, reporting all results including those which are negative, and using appropriate data analysis. In the 60 evoked potential/ERP publications evaluated by Kotchoubey, only five percent satisfied all of these criteria.

3.11.1 Sample Size

Kotchoubey (2017) expressed concerns about inadequate sample sizes and the dangers of over-interpreting studies with inadequate power, as small sample sizes result in broad confidence intervals. In DoC studies, it is not easy to recruit participants given the rarity of the condition. Further, people transition from UWS/VS to MCS and study numbers are reduced by attrition. Kotchoubey recommended that DoC researchers recruit a minimum of 25 patients from each of the UWS/VS and MCS categories and suggested that studies that are underpowered should candidly describe their outcomes as ‘preliminary results’. Kotchoubey acknowledges that it is difficult to define the exact optimum sample size for EP/ERP studies because parameters such as variance are unknown.

3.11.2 Establishing the Most Accurate Clinical Diagnosis

Kotchoubey and Pavlov (2018) discuss the issue that in DoC, there is a strong circular component undermining the evaluation of diagnostic technology and tactics. They describe how neurophysiological techniques are developed to complement clinical measures which lack sensitivity but ironically, these same clinical measures are used evaluate the novel techniques. The lack of a gold standard for diagnosis makes evaluating the efficacy of new technology very challenging.

Seel et al (2010) chaired a task force to provide evidence-based recommendations for clinical practice and research. In this document 13 DoC scales were evaluated. Only the CRS-R was recommended, and even that scale was recommended with moderate reservations. In the records evaluated by Kotchoubey and Pavlov (2018) only 29 (61.7%) employed the CRS-R. However, over the past five years, there has been an ever-increasing trend to rely on the CRS-R as a common data element in studies pertaining to DoC. Pincherle and colleagues (2019) have proposed a revision to the Motor Behavior Tool (Pignat et al, 2016) intended to complement the CRS-R (Giacino, Kalmar & White, 2004) by better detecting subtle motor behaviors.

3.11.3 Reporting All Methodological Details

Kotchoubey and Pavlov (2018) specify that a major problem in brain data outcome research in DoC is the quality of the reporting. Recently, Hicks et al. (2013) recommended core, basic and supplementary common data elements for severe brain injury that span the continuum of care which should help researchers identify key features to report and promote comparisons between studies. Of the 47 records evaluated by Kotchoubey and Pavlov (2018), which include but are not specific to ERP research, none provided a flow chart depicting patient selection. Patient selection was described in 62% of the studies but only 19.1% specified inclusion/exclusion criteria. For DoC research, it is vital to precisely detail every aspect of the study methodology and procedure. This is particularly true for ERP work given the range of possible paradigms, montages, and hard/software. Further, the prognostic and diagnostic utility of the tactics can differ for traumatic and non-traumatic populations and therefore, these patient groups must be considered separately.

Another important methodological limitation of the studies was inadequate examiner blinding. In their systematic analysis, Kotchoubey and Perrin (2018) found only two groups of authors clearly indicated that the diagnosis of outcome was performed by neurologists without the knowledge of predictor values. The authors argue that because the diagnosis between UWS and MCS is so difficult, access to any prior positive or negative neurophysiological information could bias the diagnostic decision. In more than 80% of the studies, the neurologists who evaluated the patients' outcomes were familiar with the results of neurophysiological tests and could have therefore been biased by this knowledge.

3.11.4 Publication Bias

Publication bias was also a concern identified in the systematic review by Kotchoubey and Pavlov (2018) who demonstrated that the data show a trend to selective publication of strong but unreliable results. Kotchoubey (2017) stresses the need to publish both positive and negative results. He also criticizes excessive use of qualitative reviews as this literature selectively report results and methods which can mislead the reader and complicate the interpretation of data.

3.11.5 Appropriate Data Analysis

As it is still unclear which variables in combination affect results, Kotchoubey (2017) urges authors to perform meta-analyses and use strict analytical methods that include either multivariate or joint univariate techniques.

3.12 Conclusions

This review discussed how evoked and long-latency auditory and visual event-related potentials have been used to examine brain responsiveness after severe neurological injury. Convergent literature suggests that intact SSEPs combined with MMN and pupillary light reactivity (Fischer et al., 2006), emergence of MMN between two specified test times (Tzovara et al., 2013) and presence of P300 (Daltrozzo et al. 2007) predict survival and awakening from coma. Although these factors may predict awakening, a recent multi-centre longitudinal study demonstrated that intact N20 SEP at three months did not improve the chance patients would transition from UWS to MCS by six months. Conversely, moderately abnormal to normal EEG background activity and the presence of P300 responses at three months predicted better outcomes at six months (Estraneo, et al., 2019).

Using long-latency ERPs for differential diagnosis between UWS and MCS is controversial. Auditory and visual ERP evaluation may be a useful adjunct to a more complete diagnostic battery for patients with pervasive DoC. There is some evidence that the presence of N400 predicts better outcomes over the long term (Steppacher, et al., 2013). ERPs are more likely to predict transition from UWS to MCS than they are to predict transition from MCS to consciousness (Kotchoubey & Pavlov, 2018). In 2018, a comprehensive systematic review was completed to update the 1995 American Academy of Neurology practice parameter for persistent vegetative state and the 2002 case definition for MCS for DoC lasting greater than 28 days (Giacino, et al. 2018). This document clearly demonstrates that no diagnostic assessment procedure has strong, or even moderate, evidence for use. It highlights the gaps in knowledge related to prognosis and particularly, diagnosis. The group stressed that the largest barrier to validating a more precise diagnostic approach is the lack of a gold standard with acceptable sensitivity and specificity to enable comparisons with novel techniques.

3.13 Future Directions

Based on the best available evidence (extensive literature review and the clinical experience of a group of neurophysiologists trained in the management of comatose patients), André-Obadia and colleagues (2018) developed a flowchart detailing the EEG, evoked potential, and ERP processes recommended for predicting awakening in cases of DoC caused by anoxia (see Figure 2). Clear and sequential flowcharts of this nature are also required for predicting survival, awakening, and recovery for traumatic brain injury. In the future, the goal will be to discover the best combination of imaging and electrophysiological measures for predicting the transition between altered levels of consciousness and for differentiating between those levels. For each patient group (traumatic and non-traumatic), the flowcharts need to specify the indications/contraindications for each type of diagnostic procedure, optimal timelines for testing and re-testing, ideal stimuli and paradigm options, and data collection/analysis parameters.

As previously mentioned, several DoC methodological issues limit the interpretability of ERP studies and reports. A primary concern, small sample sizes, compromises the power of studies. It seems logical that multiple national and perhaps even international sites need to undertake coordinated research initiatives to ensure adequate sample sizes. Pascarella and a large group of colleagues (2018) describe a multicentre prospective registry for patients with DoC admitted to ten intensive rehabilitation units and describe the importance of a registry for collecting high quality data through the application of rigorous methods. Multicentre collaboration and an expanded national or international registry of this nature could dramatically improve sample sizes and continuity of patient care.

This review highlights the need to improve the quality of studies and provide more detailed methodology summaries. In the future, research must consider and address these shortcomings. DoC researchers are challenged to use analysis strategies that allow multivariate or joint univariate comparisons to enable more definitive conclusions regarding the utility of specific or combined evoked potential and ERP measures. In addition, it is vital to follow patients longitudinally so that long-term outcomes can be ascertained. Finally, it appears imperative that, until more information is available, all studies in patient populations include the CRS-R (Giacino, Kalmar & White, 2004) complemented by the revised Motor Behavior Tool (MBT-r) described by Pincherle and colleagues (2019) to improve the chance of detecting cognitive motor dissociation (covert cognition) at the bedside (Schiff, 2015).

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Appendix 1: Primary Database Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to current>

#	Search Statement
1	conscious*.mp. or exp Consciousness/
2	exp Awareness/ or awareness*.mp.
3	thinking.mp. or exp Thinking/
4	thought.ti,ab.
5	exp Cognition/ or cognition.mp.
6	cognitive.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	(evok* adj2 potential*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9	verp.mp.
10	exp Evoked Potentials, Somatosensory/ or exp Evoked Potentials, Auditory/ or sser.mp.
11	cep.mp.
12	"locked in syndrome*".mp.
13	exp Persistent Vegetative State/ or exp Consciousness Disorders/ or minimal* conscious*.mp.
14	(consciousness adj2 disorder*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15	vegetative state$.mp.
16	(coma or comas or comatose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17	exp Coma/ or unresponsive wakefulness.mp.
18	8 or 9 or 10 or 11
19	12 or 13 or 14 or 15 or 16 or 17
20	7 and 18 and 19
21	eeg.mp. or exp Electroencephalography/
22	Electroencephalography.ti,ab.
23	exp Neuroimaging/ or exp Magnetic Resonance Imaging/ or neuroimag*.mp.
24	fmrt.mp.
25	exp Transcranial Magnetic Stimulation/ or tms.mp.
26	21 or 22 or 23 or 24 or 25
27	7 and 19 and 26
28	20 and 27

Chapter 4 (Publication 1):

Clinical Applications of The HCS: Tracking Recovery in Severely Brain Injured Patient

Carolyn Fleck-Prediger[1, 2], Sujoy G. Hajra[3,4], Bruce D. Dick[1,5], D. Shaun Gray[1,2,6], Careesa C. Liu [3,4], Lauren Petley[7], and Ryan C.N. D'Arcy[*3,4]

[1]Neuroscience and Mental Health Institute, University of Alberta, Alberta, Canada; [2]Halvar Jonson Centre for Brain Injury, Ponoka, Alberta, Canada; [3]Schools of Engineering and Computing Sciences, Simon Fraser University, British Columbia, Canada; [4]Surrey Memorial Hospital, Fraser Health Authority, British Columbia, Canada; [5]Departments of Anesthesiology and Pain Medicine, Psychiatry & Pediatrics, University of Alberta, Alberta, Canada; [6]Division of Physical Medicine and Rehabilitation, University of Alberta, and Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada; [7]Biomedical Translational Imaging Centre, IWK Health Centre and QEII Health Sciences Centre, Halifax, Nova Scotia, Canada

*Corresponding author: Simon Fraser University, Faculty of Applied Sciences School of Engineering Science, School of Computer Science, 250-13450 102nd Ave, Surrey, BC, Canada, V3T 0A3, 778-782-9190 (Telephone), 778-782-8116 (Fax)

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Chapter 4 (Publication 1):

Abstract

Severe neurological damage can cause speech and movement limitations that mask preserved cognitive capacities and create challenges differentially diagnosing persistent vegetative, minimally conscious and “locked-in” states of consciousness. Significant practical challenges impede both the initial clinical evaluation of consciousness and ongoing appraisal of patient status over time. By necessity, clinical evaluation currently relies on observation of conscious awareness to estimate the functional repercussions of severe brain injury. This can lead to misdiagnosis when ‘mind-motor disconnection’ renders patients unable to demonstrate their capacities. The Halifax Consciousness Scanner (HCS) uses auditory event-related brain potentials (ERPs) to measure neural responses during information processing, without relying on overt behavioral responses. Here we describe this emerging neurotechnology using an illustrative case in an inpatient rehabilitation setting. In this case, the initial HCS profile demonstrated intact pre-linguistic capacities but impaired receptive language. Over time and with treatment, the patient’s HCS language response progressively improved and most importantly here, these progressive HCS changes coincided with clinical progress.

Chapter 4 (Publication 1):

4.1 Introduction

After severe brain injury, disorders of consciousness (DoC) such as persisting post-coma unawareness or unresponsive wakefulness syndrome (the so-called vegetative state), minimally conscious state, or even locked-in state, may persist well beyond the acute phases of injury. The clinical challenge is to accurately diagnose the correct DoC and monitor information processing as a reflection of functional status. Correct differential diagnosis is essential in order to identify the patients with the greatest potential for recovery as recent studies demonstrate substantial ongoing recovery in minimally responsive patients continuing up to two years post-injury with more modest potential for improvement following this period, up to five years post-injury (Nakase-Richardson et al., 2012). The problem can be separated into at least two inter-related challenges: 1) accurate initial level of awareness evaluation; and 2) ongoing monitoring of changes over time and with treatment.

4.2 Initial Evaluation

There is a pressing need for enhanced objective evaluation and concrete diagnosis at the earliest stages of the critical care cascade. Up to 43% of patients with DoC were misdiagnosed as being in a vegetative state in one series (Andrews, K., Murphy, Munday, & Littlewood, 1996). Severely injured patients often experience communication limitations and immobility that mask preserved cognitive capacities (Connolly, D'Arcy, Lynn, & Kemps, 2000). It is becoming clear that conscious experience may well exist without overt behavioural signs of conscious awareness (Wijnen, van Boxtel, Eilander, & de Gelder, 2007).

4.3 Treatment Monitoring

An injured brain is particularly plastic and this neuro-modulation can be adaptive or maladaptive, depending on the quantity and quality of experience (Nudo, 2013). In stroke rehabilitation, enriched environments have been shown to improve social engagement in patients (Janssen et al., 2014). Given the evidence supporting neuroplastic change and environmental enrichment, early responsiveness to intervention and probability of rehabilitation success needs to be assessed. While behavioral assessments will always be necessary, paralysis and apraxia can mask a patient's true status and gains which hampers care planning and the provision of rehabilitation in this population. Further, these patients are not well followed over time which limits prognostication.

4.4 Neurotechnology Tools

Advances in functional neuroimaging and related neurotechnologies are creating possible solutions to evaluation challenges outlined above (Gawryluk, D'Arcy, Connolly, & Weaver, 2010). An emerging neurotechnology, the Halifax Consciousness Scanner (HCS) developed by D'Arcy, Hajra, Liu, Sculthorpe, & Weaver (2011), uses auditory event-related brain potentials (ERPs) to measure neural responses during information processing using rapid and easily deployable electroencephalography (EEG) techniques. Foundational work for this technology has demonstrated the utility of ERPs in evaluating a range of functions (sensory to cognitive) in neurological patients who experience concomitant problems with communication [Connolly et al., 2000; Connolly & D'Arcy, 2000; D'Arcy et al., 2003).

ERPs are frequently used to understand how the brain processes information in real time with temporal resolution at the level of milliseconds (Gawryluk et al., 2010; Luck, 2005)] and are particularly useful as brain responses related to information processing are captured *without* relying on overt behavioural responses. Furthermore, EEG-based techniques are non-invasive, easy to administer, and inexpensive making them practical, accessible, and easy to integrate into treatment.

D'Arcy and colleagues (2011) provide an overview of HCS ERP methods. In brief, the system uses variants of well-established ERPs that cover the spectrum of information processing. Target ERPs are extracted by presenting a series of stimuli and averaging the associated EEG activity to isolate the signal resulting from the brain's response to the stimuli from the overall background EEG 'noise'. The two components of interest here are the P300, a measure of attention (Polich, 2003) and the N400, a measure of semantic processing and comprehension (Kutas & Hillyard, 1980). Recording electrodes cover the midline anterior-posterior axis (Fz, Cz, Pz). ERP components are obtained using a 5-minute auditory stimulus sequence that combines tones (2.5 minutes) and speech (2.5 minutes). Through earphones, tones of varying intensity and pattern are presented. The

600 tone sequence is comprised of two spectrally rich tones (A and B). Standard tones are presented in an alternating pattern (ABABAB...) with an intensity of 75 dB SPL. The stimuli contain occasional deviant stimuli consisting of repetition deviants (repetitions of either the A or the B tone, e.g., ABABBBA) and intensity deviants which follow the standard alternating pattern of the sequence but have an intensity of 100 dB SPL. Occasional deviant stimuli, particularly intensity deviants, evoke the P300.

After the tone stimuli, participants hear 30 phrases that build sentences with 'semantic expectation.' Each phrase is presented twice – once with a congruent ending and once with an incongruent ending. The N400 is elicited maximally by the incongruent endings. For example, the phrase "The pizza is too hot to ____" builds an expectation for the congruent terminal word "eat" in comparison to the incongruent terminal word "sing". The phrases begin with either the subject's own name or a control name with no personal relevance. These two names are distributed randomly among the phrases. Signal-averaged responses for each indicator are calculated to generate a final "consciousness score". By comparing patient results to norms, basic cognitive status is revealed. The condensed nature of the screening is critical for easily fatigued, severely injured patients. The HCS protocol also enables rapid bedside testing to minimize interruptions to patient care.

4.5 Case Study: HCS Clinical Application Examined

4.5.1 The Case

FM, a 45-year-old male, sustained an assault resulting in severe traumatic brain injury with an initial Glasgow Coma Scale of 3T. Imaging revealed intracerebral hemorrhage involving the left frontobasal portions of the brain from the upper basal ganglia to corona radiata. He required a craniotomy and ventricular drain. FM was admitted to rehabilitation 7-months post-injury with an altered but undetermined level of conscious awareness. Initial HCS screening was completed 20 days post-admission. At this time, FM's GCS was 9/15 (4 Eyes, 1 Verbal, 4 Motor). He was dependent on a gastrostomy feeding tube and required suction oral care. He was unable to maintain an upright posture without support and was entirely dependent for bed/wheelchair mobility. FM demonstrated little awareness of his environment and his gaze was fixed to the upper left quadrant. He did not follow instructions, speak or communicate his needs. In view of this, great debate ensued amongst his caregivers regarding his capacity to process information. This debate was further fuelled by the fact that he was able to spontaneously move his left arm but could not follow any motor commands with this limb.

4.5.2 The Process

Prior to HCS testing, Otoacoustic Emission (OEA) and Auditory Brainstem Response (ABR) tests were conducted. FM's OEA results were normal, but ABR was highly confounded by tone and muscle twitches. Unlike the HCS, the ABR instrumentation could not effectively eliminate noise artifact. FM clearly demonstrated auditory capacity, as he startled to unexpected, out of sight noise. Over the treatment period, FM underwent three HCS testing sessions to evaluate brain function and monitor electrophysiological changes. Figure 1 shows ERPs responses for FM and a typical healthy control for comparison.

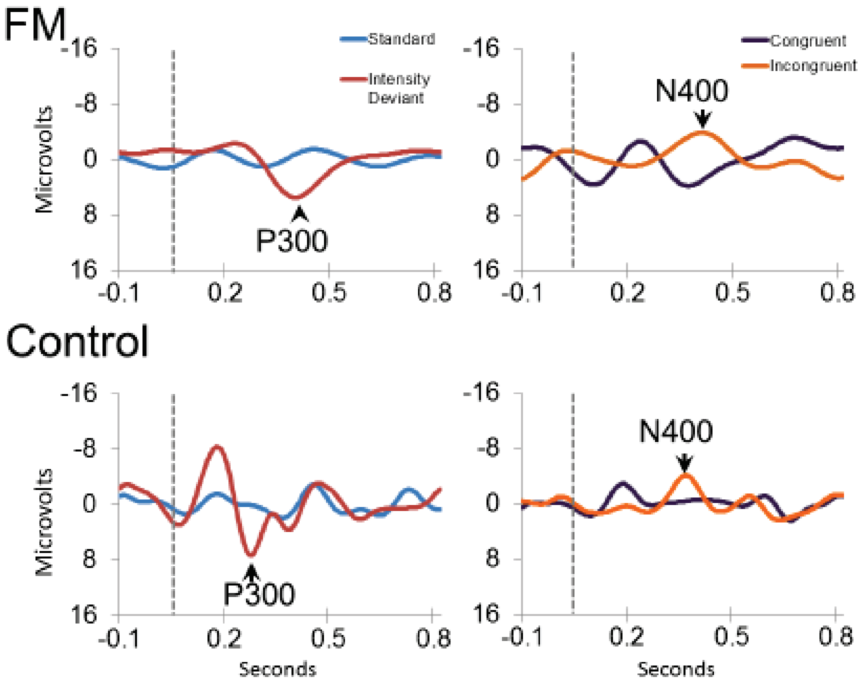

Figure 1: HCS ERP Responses (P300 & N400) in Patient versus Healthy Control

Figure shows HCS ERP responses – the P300 (left) to intensity deviant and the N400 (right) to incongruent word in FM (top) and a healthy control (bottom). Time is on the horizontal axis (seconds) and response size and polarity is on the vertical axis (microvolts).

4.5.3 Results

Pre-treatment: Level of comprehension was unknown. In pre-treatment testing, basic sensation and perception indicators were present (N100 and mismatch negativity, respectively). Consistent P300 responses to deviant tones were observed, reflecting ‘automatic’ attention responses. However, in pre-treatment tests, the N400 response was equivocal, suggesting impaired semantic processing and comprehension. Given that FM possessed basic sensory and attention capacities but impaired auditory comprehension, he received intensive speech-language intervention focusing on receptive language. Messages were relayed to him in simplified language and verbal messages were augmented with printed words, drawings, pictures, hand gestures and demonstrations. As treatment progressed, FM’s engagement improved slowly. HCS testing at 7-months post-admission verified that, despite persistent communication limitations, his receptive language had improved. Specifically, HCS testing revealed the emergence of the N400 response.

Post Treatment: On post-treatment tests (11 months post-admission), FM’s semantic processing and comprehension performance was within normal limits as measured by a clear N400 response on the HCS. Figure 2 shows no change in FM’s P300 across three test sessions, while there is a statistically significant ($p < 0.05$) re-emergence of the N400 response (Figure 3).

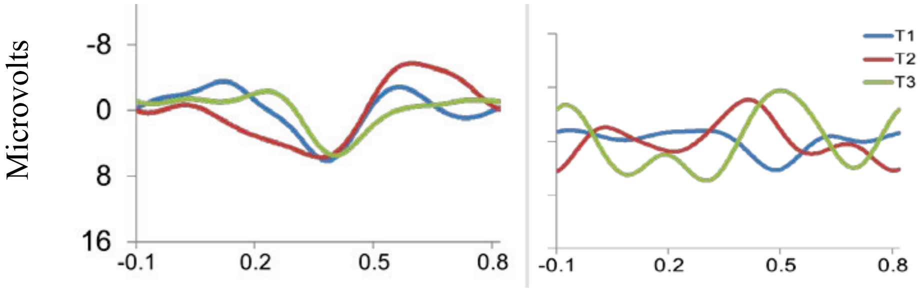

Figure 2: P300 & N400 at 3 Time Points for Patient

Figure shows P300 (intensity deviant) and N400 (incongruent word) components measured at 3 time points for FM. The P300 responses to are consistent across the 3 time points. In contrast, the N400 responses increase across the 3 time points. All other details as in Fig. 1.

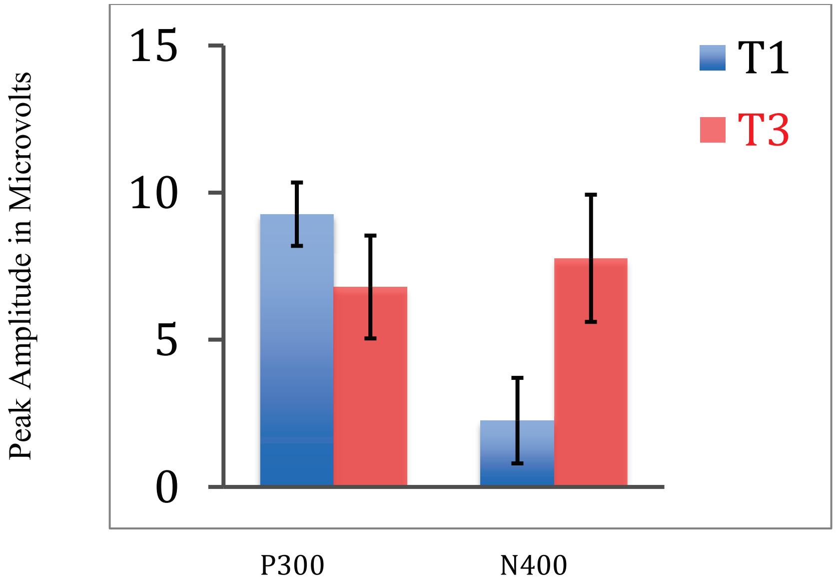

Figure 3: Patient P300 & N400 Differences Between Time Points

Figure shows P300 (intensity deviant) and N400 (incongruent word) differences between T1 and T3. Mean ± SE. *p<0.05.

4.5.4 Clinical Outcomes

FM made significant cognitive and physical gains during treatment. While an inpatient, FM learned to use his left hand to communicate a limited set of functional gestures. ‘Motor-mind disconnectedness’ continued to be a significant barrier to intentional movement and speech. Occasionally, FM sang and spoke in short phrases, which were intelligible in context. He intermittently responded to humor. He became able to safely consume food and fluid orally. He learned to feed himself with close supervision. He recognized familiar people. FM was able to reposition himself in bed, sit unsupported at bedside for short periods, and mobilize short distances in a manual wheelchair (single left arm and bilateral leg propulsion). Despite mobility gains, he continued to require encouragement to move due to residual initiation deficits. He became attentive to the right visual field and was no longer locked in an upward left gaze. FM was discharged to a community residential setting. Shortly after discharge, his gastrostomy tube was removed. At 6 months post-discharge follow-up, his family reported that he had maintained his gains and continued to demonstrate slow, steady physical and cognitive improvements.

4.5.5 HCS Impact on Practice

The HCS testing results provided critical information for both initial evaluation and monitoring of treatment progress. Initial evaluation demonstrated that FM had intact attention (P300) but impaired comprehension (N400). Appreciating comprehension limitations helped to define speech-language treatment goals and enabled appropriate inter-disciplinary therapists/family member interactions. During intensive treatment, serial HCS monitoring revealed receptive language gains, as indexed by the emergence of the N400 response. These results helped justify continued specialized rehabilitation over an eleven-month period. The HCS results provided critical information about FM's functional information processing status to his family, treatment team, and healthcare funders.

4.6 Conclusion

Enriched (versus standard) living environments trigger structural changes in the brain and enhance functional outcomes (Johansson, 2000). As demonstrated here, significant functional gains are possible when strategic rehabilitation is provided, even in very severe TBI. The HCS eliminates "motor-mind disconnection" confounds by using electrophysiology to evaluate and monitor the functional progress of patients. In this case, treatment time was not wasted in debating FM's cognitive status (i.e., initial evaluation). Advanced service and care were delivered with treatment focused on comprehension and measured in terms of the recovery of the HCS N400 response (i.e., treatment monitoring). Given the challenges in objective evaluation and monitoring of conscious awareness, there are understandable difficulties in accurately discriminating the relevant DoC (vegetative versus minimally conscious versus locked-in states) and therefore planning for appropriate rehabilitation and ongoing care. This difficulty in accurately diagnosing disorders of consciousness has confounded not only clinical care but even attempts to understand the prevalence of vegetative and minimally conscious states (Pisa, Biasutti, Drigo, & Barbone, 2014). ERP techniques such as the Halifax Consciousness Scanner may provide an inexpensive, non-invasive, valid, and reliable bedside method of assessing cognitive processing in patients with disorders of consciousness. We would agree with Duncan, Summers, Perla, Colburn & Mirsky (2011) that "It is likely that the use of ERPs in evaluating and planning the treatment of TBI survivors will become standard clinical practice". We believe that our case study not only offers proof of this general concept but also aided significantly in improving the rehabilitation outcome for our patient. Given the ability of ERPs to signal learning even before overt signs of task improvement are seen in healthy individuals (McLaughlin, Osterhout, & Kim, 2004; Atienza, Cantero, & Dominguez-Marin, 2002), it is possible that frequent ERP testing in brain injured patients could provide evidence of neuroplastic changes to help optimize rehabilitation even before gains are clinically observed. Further studies evaluating ERP-based neuro-technologies in larger patient samples with significant motor and/or communication impairments after moderate to severe acquired brain injury are underway.

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Disclosures

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Chapter 4 (Publication 1):

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Chapter 5 (Publication 2)

Point of care brain injury evaluation of conscious awareness: Wide scale deployment of portable HCS EEG evaluation

*Carolyn M. Fleck-Prediger[1,2], Sujoy Ghosh Hajra[3,4], Careesa C. Liu[3,4], D. Shaun Gray,[1,2,5], Donald F. Weaver[6], Shishir Gopinath[4], Bruce D. Dick[1,7], & Ryan C.N. D'Arcy[3,4] **

[1]Neuroscience and Mental Health Institute, University of Alberta, Canada, [2]Halvar Jonson Centre for Brain Injury, Canada, [3]Faculty of Applied Sciences (Engineering Science and Computing Science), Simon Fraser University, Canada, [4]NeuroTech Lab, Simon Fraser University and Fraser Health Authority, Surrey, BC, Canada, [5]Division of Physical Medicine and Rehabilitation, University of Alberta, Canada, [6]Krembil Research Institute, UHN, University of Toronto, Canada, [7]Departments of Anesthesiology and Pain Medicine, Psychiatry & Pediatrics, University of Alberta, Canada

*__Corresponding author__: Simon Fraser University, Faculty of Applied Sciences School of Engineering Science, School of Computer Science, 250-13450 102nd Ave, Surrey, BC, Canada, V3T 0A3, 778-782-9190 (Telephone), 778-782-8116 (Fax)

Key words: Disorders of Consciousness, EEG, ERP, Halifax Consciousness Scanner, P300

Abbreviations: Coma Recovery Scale – Revised (CRS-R), Disorders of Consciousness (DoC), electroencephalography (EEG), event-related potentials (ERPs), Glasgow Coma Scale (GCS), Halifax Consciousness Scanner (HCS), level of consciousness (LOC), locked-in state (LIS), minimally conscious state (MCS), non-traumatic brain injury (n-TBI), Point-of-Care (POC), traumatic brain injury (TBI), vegetative state (VS), unresponsive wakefulness syndrome (UWS)

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Abstract

Survivors of severe brain injury may remain in a decreased state of conscious awareness for an extended period of time. Clinical scales are used to describe levels of consciousness but rely on behavioural responses, precipitating misdiagnosis. We have previously utilized event-related potentials (ERPs) to circumvent reliance on behavioural responses. However, practical implementation barriers limit the clinical utility of ERP assessment at point-of-care. To address this challenge, we developed the Halifax Consciousness Scanner (HCS) - a rapid, semi-automated EEG system. The current study evaluated: 1) HCS feasibility in sub-acute, point-of-care settings nationwide; 2) ERP P300 responses in patients with acquired brain injury versus healthy controls; and 3) Correlations within and between clinical measures and P300 latencies. *Methods:* We assessed 28 patients with severe, chronic impairments from brain injuries and contrasted the results with healthy control data (n=100). Correlational analyses examined relationships between P300 latencies and the commonly used clinical scales. *Results:* P300 latencies were significantly delayed in patients compared to healthy controls ($p<0.05$). Clinical assessment scores were significantly inter-correlated and correlated significantly with P300 latencies ($p<0.05$). *Conclusions:* In sub-acute and chronic care settings, the HCS provided a physiological measure of neurocognitive processing at point-of-care for patients with severe acquired brain injury, including those with disorders of consciousness.

5.1 Introduction

After serious neurological injury, patients may die, remain in coma, or awaken as evidenced by eye opening. Those who awaken may remain in a state of environmentally unresponsive wakefulness, improve to a minimally conscious state (MCS) with clear but intermittent and inconsistent signs of self and environmental awareness, or regain full conscious awareness (Di Perri et al., 2014). Edlow and colleagues (2017) suggest that early detection of masked consciousness and cortical responses could inform life-altering clinical decision-making. However, medical complications and the related interventions often impede accurate evaluation of consciousness (Giacino, Katz, & Whyte, 2013). Given these confounds, assessing a patient’s level of consciousness (LOC) too early may misinform clinical decision-making at the top of the critical care cascade. During acute phases, many patients may truly be incapable of functional information processing but in some cases, consciousness gradually recovers. This cognitive recovery can happen with or without the development of motor capacities and behavioural output. In view of this and the fact that subtle changes can go unnoticed in busy long-term care settings, Giacino, Fins, Laureys and Schiff (2014) stress the importance of an integrated system of care that responds to the needs of patients as they evolve.

Clinical assessments such as the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) and CRS-R (CRS-R) (Giacino, Kalmar & Whyte, 2004) rely on the subjective observation of patient responses without considering patient or situational variables (Reith, Brennan, Maas, & Teasdale, 2016). Scales that are solely based on observation of patient responses misdiagnose certain patients because consciousness can exist without behavioural signs. In fact, as Wijnen, van Boxtel, Eilander, & de Gelder (2007) point out, patients who remain in an unresponsive wakeful state do not score worse on early motor-based assessment scales than those who eventually regain some degree of conscious awareness. Andrews, Murphy, Munday, & Littlewood (1996) examined patients on a rehabilitation unit with the working diagnosis of vegetative state and found the misdiagnosis rate to be as high as 43%. Importantly, once conscious awareness was detected, nearly all of these patients were able to relay choices regarding quality of life issues using alternate means of communication. Despite the growing recognition of this important problem, Schnakers and colleagues (2009) showed that the rate of misdiagnosis did not change substantially over the 15-year period following the study by the Andrews group remaining at over 40%. This situation underscores the need for objective physiological measurement tools that bridge the gap between research evidence and clinical implementation. Solutions are emerging from brain imaging technologies that track physiological responses and these tactics are being translated to sub-acute rehabilitation settings. Fleck-Prediger and colleagues (2015) used the HCS in a TBI case study to evaluate ERP changes during active speech language rehabilitation. In this single case study, P300 results remained stable while the response size of a latter ERP component, the N400, improved in parallel with significant clinical improvement in auditory comprehension.

A number of groups, including ours, have used brain imaging technologies such as EEG/ERPs, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) to explore DoC (Bodart et al., 2015; Casali et al. (2013); Gawryluk, D'Arcy, Connolly, & Weaver, 2010; Harrison & Connolly, 2013; Laureys, Owen, & Schiff (2004); Owen et al., 2006; Ragazzoni et al., 2013; Sitt et al., 2014). While these various brain-imaging technologies have contributed valuable insights, one of the major practical challenges has been clinical implementation in front-line point-of-care (POC) settings. To address this, we developed a portable, semi-automated EEG device, the Halifax Consciousness Scanner (HCS), for user-friendly ERP testing (D'Arcy, Ghosh-Hajra, Liu, Sculthorpe, & Weaver, 2011). The HCS provides an objective, rapid POC approach and has been separately validated across a large sample of healthy controls Sculthorpe-Petley et al., 2015.

With advances in portable EEG devices, ERPs are increasingly being used to investigate conscious awareness (Cruse et al., 2011; D'Arcy et al., 2011; Fleck-Prediger et al., 2015; Guger et al., 2017; Hinterberger, Wilhelm, Mellinger, Kotchoubey, & Birbaumer, 2005). Emerging from clinical ERP assessment work that began the mid-1990s (Connolly & D'Arcy, 2000; Connolly, D'Arcy, Newman, & Kemps, 2000; Connolly, Mate-Kole, & Joyce, 1999; Connolly, Phillips, & Forbes, 1995; D'Arcy et al., 2003; Hajra et al., 2016) the objective of the HCS was to integrate a range of ERP components into a rapid, semi-automated evaluation for POC. Any one or more of these ERP components could then be utilized for neuroscience evaluations from low-level sensation to higher-level language and cognition. With the HCS normative study complete (Sculthorpe-Petley et al., 2015) and preliminary case study evidence (Fleck-Prediger et al., 2015), patient studies that evaluate the practical applications of this ERP assessment across different DoC POC sites are underway to further develop and validate the technology. In this study, the compressed HCS enabled evaluation of the relationship between auditory evoked P300 responses and subjective clinical DoC measures (i.e. rating scales). In order to ensure scientific rigor and avoid spurious conclusions, we purposefully targeted a single robust measure appropriate for complex patient data (i.e. P300 latency). We systematically required the presence of the N100 to validate auditory sensation and then tested the null hypothesis that the P300 latency (as a neural measure of information processing) would not show a significant relationship with the clinical rating scales.

The P300, an objective, physiological measure of information processing, is a positive endogenous component with a prototypical peak 300 ms after stimulus onset, usually between 250-500 ms but this range can vary with the stimulus modality (Polich, 2007). It is thought to serve as a temporal measure of the neural activity underlying the allocation of attention and immediate memory processes (Polich & Heine, 1996). In simple tasks, the P300 amplitude is typically large and its latency is short in duration. However, as task demands increase, the amplitude decreases and the peak latency lengthens because processing resources must be dedicated to task completion (Kok, 2001). Therefore, we anticipate the P300 latency will be delayed in DoC patients (relative to normative data) and will correlate negatively with the patients' measured state of conscious awareness using standard clinical tests. As Steppacher, Eickhoff, Jordanov, Kaps, Witzke, & Kissler (2013) have shown, this does not to imply that P300 has significant predictive powers regarding the re-emergence of consciousness. Rather, this simply establishes the P300 as a neural indicator of information processing in patients with lower levels of conscious awareness.

Research and rehabilitation communities often do not adequately monitor patients over time and therefore may not detect subtle changes in conscious awareness. The need for serial monitoring is based on an increasing understanding that patients can demonstrate substantial recovery over long periods of time. For example, Nakase-Richardson and colleagues (2012) studied acute and long-term outcomes from DoC and found that two-thirds of patients regained the ability to follow commands during rehabilitation and one-fourth emerged from post-traumatic amnesia. Furthermore, significant recovery continued for two years post-injury with more modest gains for as long as five years post-injury. We have also reported on a 3-year case control study in which a severe TBI survivor recovered from coma to demonstrate continued recovery of motor function and corresponding functional MRI activation changes well past 6-years after injury (D'Arcy et al., 2016).

5.2 Objectives and Hypothesis

We conducted a validation study to test the HCS in clinical, sub-acute acquired brain injury settings nationwide. The objectives were to 1) evaluate the feasibility of HCS testing at POC centres nationwide; 2) compare the P300 response generated by HCS to normative data; and 3) examine the correlations within and between clinical scales to P300 latencies. It was hypothesized that: 1) patient P300 latencies would be delayed relative to healthy control normative data; 2) that the GCS, CRS-R, and Functional Independence Measure (FIM) clinical scales would be significantly inter-correlated; and 3) patient P300 latencies would also be significantly correlated with the above clinical scales, demonstrating an important relationship with functional impairment.

5.3 Methods

5.3.1 Participants

EEG testing was attempted on twenty-eight (28) adults with severe neurological injury at diverse points-of-care across Canada (Figure 1a). Caregivers or therapists referred patients, and preferentially included those patients suspected to have some degree of awareness. The EEG quality was sufficient to evaluate HCS results in twenty of the cases. HCS results from the remaining eight participants were not analyzed due to: hearing impairment (n=1), poor signal quality/extreme environmental and/or muscle movement artefact (n=5), or technical failure (n=2) (Table 1). All participants had sustained severe acquired brain injury (traumatic or non-traumatic including anoxia) or stroke (haemorrhagic or ischemic) with a GCS of 8 or less in the acute phase (Table 2). Participants were medically stable but chronically impaired. There was heterogeneity in terms of age (Table 1 and Figure 1b), etiology (Table 1and Figure 1c), time elapsed since injury or event (Table 1), level of responsiveness (Table 3), and rehabilitation opportunity. Twenty-five percent of these participants were fully conscious but experienced persistent and severe motor, communication and cognitive sequelae consequent to their neurological injury. The remaining 75% of the participants were classified as either being comatose, unresponsive but wakeful, partially/inconsistently responsive, or fully responsive based on clinical observations and the administration of the JFK Coma Recovery Scale-R (CRS-R). Although our clinical categories were informed by using the CRS-R, we purposefully avoided categorizing the patients into the firm unresponsive wakeful syndrome (UWS) or minimally conscious state (MCS) divisions described by the CRS-R, as the goal was to differentiate between broad levels of responsiveness using an objective, physiological measure not to assign patients to specific diagnostic categories.

Figure 1a: Test Locations

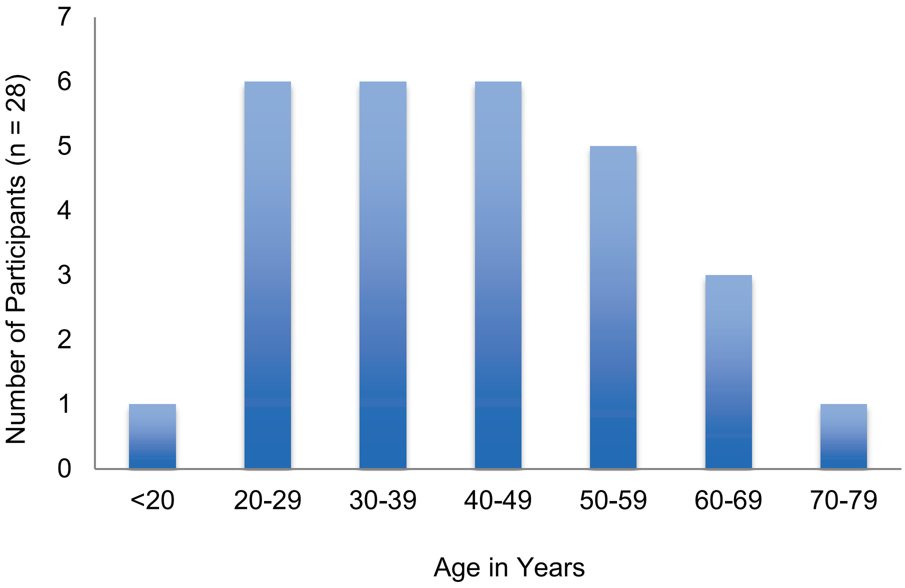

Figure 1b: Bar graphs of Participant Ages

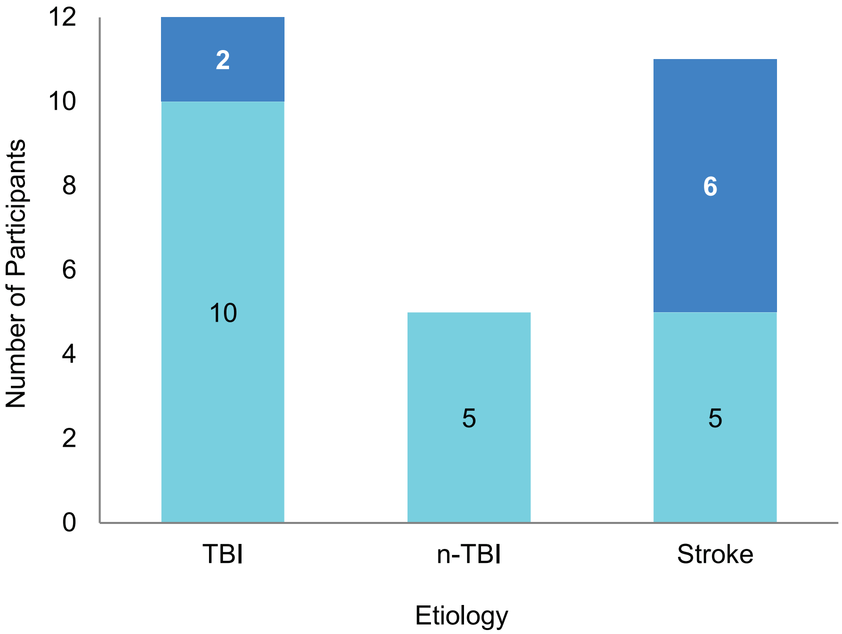

Figure 1c: Participants Tested/Excluded in Etiology Categories

Table 1 Demographics of Participants and Rationale for Exclusions

#	Sex	Age	Etiology	Time Post	#	Sex	Age	Etiology	Time Post
1	M	43	TBI	38 m	**2**	M	22	TBI	15 m
3	M	26	n-TBI	44 m	**4**	F	67	Stroke	35 m
5	M	57	TBI	98 m	**6**	M	30	n-TBI	31 m
7	M	34	n-TBI	199 m	**8**	F	64	Stroke	214 m
9	M	45	TBI	7 m	**10**	F	43	TBI	19 m
11	M	55	Stroke	20 m	**12**	F	54	Stroke	20 m
13	M	27	TBI	12 m	**14**	M	46	TBI	62 m
15	M	35	TBI	54 m	**16**	F	24	TBI	11 m
17	M	18	TBI	27 m	**18**	M	57	Stroke	6 d
19	F	36	n-TBI	130 m	**20**	M	71	n-TBI	11d

Exclusions:

#	Behavioral Diagnosis	Exclusion Reason	#	Behavioral Diagnosis	Exclusion Reason
21	Conscious	Environmental Artefact	**22**	Conscious	Environmental Artefact
23	Conscious		**24**	Conscious	
25	Conscious	Cranioplasty	**26**	Conscious	Poor Hearing
27	Conscious	ERP trigger issues	**28**	Conscious	ERP trigger issues

Table 2: Time to Testing Information and Clinical Scores (CRS-R and GCS)

Etiology	n	Time to Testing [Range], $\overline{x}$, σ	CRS-R [Range], $\overline{x}$, σ	GCS at Injury [Range], $\overline{x}$, σ	GCS at Testing [Range], $\overline{x}$, σ
TBI	10	[7 m - 8.2 y] $\overline{x}$ = 2.9 y σ = 2.4 y	[6-22] $\overline{x}$ = 13.4 σ = 5.2	[3T-7T] $\overline{x}$ = 3.9 σ = 1.4	[7T-15] $\overline{x}$ = 9.4 σ = 2.5
n-TBI	5	[11 d - 16.6 y] $\overline{x}$ = 6.7 y σ = 6.8 y	[1-17] $\overline{x}$ = 9.8 σ = 6.7	[3T-5T] $\overline{x}$ = 3.4 σ = 0.9	[5T-12] $\overline{x}$ = 9 σ = 2.9
Stroke	5	[6 d - 17.8 y] $\overline{x}$ = 4.8 y σ = 7.3 y	[11-18] $\overline{x}$ = 12.8 σ = 3.0	[3T-7T] $\overline{x}$ = 3.8 σ = 1.8	[7T-11] $\overline{x}$ = 9 σ = 1.6
Combined	20	[6 d - 17.8 y] $\overline{x}$ = 4.3 y σ = 5.2 y	[1-22] $\overline{x}$ = 12.4 σ = 5.2	[3T-7T] $\overline{x}$ = 3.8 σ = 1.3	[5T-15] $\overline{x}$ = 9.2 σ = 2.3

Table 3: Clinical Scores and Clinical Impression of Responsiveness

#	GCS	CRS-R	Clinical Impression	#	GCS	CRS-R	Clinical Impression
1	15	4,5,6,2,2,3 (22)	Responsive	**11**	8T	2,3,3,1,0,2 (11)	Partially Responsive
2	12	4,5,6,2,2,3 (22)	Responsive	**12**	9	2,3,3,1,0,2 (11)	Partially Responsive
3	12	3,5,5,1,1,2 (17)	Responsive	**13**	8	2,3,3,1,0,2 (11)	Partially Responsive
4	11	3,5,5,2,1,2 (18)	Responsive	**14**	7T	2,3,3,1,0,2 (11)	Partially Responsive
5	11	3,5,3,1,2,2 (16)	Responsive	**15**	8	2,3,3,1,0,2 (11)	Partially Responsive
6	11	2,3,3,1,0,2 (11)	Partially Responsive	**16**	8	2,2,3,1,0,2 (10)	Partially Responsive
7	10	2,3,5,2,1,2 (15)	Partially Responsive	**17**	8	1,1,2,1,0,1 (6)	Unresponsive
8	10	2,3,5,1,0,2 (13)	Partially Responsive	**18**	7T	1,1,1,1,0,1 (5)	Unresponsive
9	9	2,3,5,2,0,2 (14)	Partially Responsive	**19**	7	1,1,1,1,0,1 (5)	Unresponsive
10	8	2,3,3,1,0,2 (11)	Partially Responsive	**20**	5T	0,0,1,0,0,0 (1)	Comatose

Except for the comatose patient, all patients who were successfully tested awoke to, startled at, or oriented towards out of sight noise - a behavioural indicator of intact hearing. Three participants received full audiology evaluations to validate candidacy.

5.3.2 Clinical Scale Scores

The GCS and JFK CRS-R scores were collected as clinical measures at the time of testing. All clinical measures were correlated with one another and with P300 latencies. P300 latencies were also correlated with the FIM on a subset of participants engaged in inter-disciplinary rehabilitation. FIM scores were included in this study as this tool is frequently used in clinical settings – even for patients who are not fully responsive. In addition, this sample included a wide variety of patients with severe brain injury, including those who were unresponsive, minimally responsive, and fully responsive and the FIM captured functional differences between the groups. As the FIM reflected, many survivors of severe brain injury regain full consciousness and compensate well for their impairments despite persistent physical impairments.

5.3.3 Instrumentation

HCS used a portable 8-channel GmobiLab EEG system (g.tec Medical Engineering, GmbH), comprised of recording electrodes, earphones, an electrode interface, an impedance monitor, and a handheld computer. Custom software automated auditory stimulus presentation (5-minute sequence) and data acquisition, with a semi-automated data analysis that was manually verified. Results were derived from three midline recording electrodes, covering the anterior-posterior axis (approximating Fz, Cz, Pz). Four other electrodes served as ground (forehead), reference (earlobe), and left and right electro-oculograms (EOG) (Connolly & Kleinman, 1978). All impedances were below 5 kΩ. The EEG and EOG signals were sampled at a rate of 256 Hz, with a band-pass of 0.1 – 100 Hz and stored for offline analyses.

5.3.4 Process

The National Research Council of Canada (NRC) and University of Alberta Human Research Ethics Board approved the study. Each patient or a legal delegate provided informed consent. During a single visit, the examiner(s) administered the HCS paradigm twice and administered clinical consciousness scales (GCS-R and CRS-R), often recruiting assistance from the rehabilitation staff and/or nursing staff familiar with the patient. An inter-disciplinary group of rehabilitation professionals collaboratively ranked the subset of patients actively participating in rehabilitation on the FIM as part of routine clinical care.

ERP analyses were completed and P300 components were both automatically identified and manually verified (SGH, CCL, & RCND). All P300 component identification results were then additionally evaluated by separate examiners blinded to patient identities and profiles (CfP and BD). Patient preparation for HCS testing involved simple instructions to listen to tones and sentences for anything unexpected.

5.3.5 Stimuli

Details of the HCS stimulus sequence have been described elsewhere (D'Arcy et al., 2011). Briefly, the HCS elicited auditory ERP components linked to sensation (N100);

perception (MMN); attention (P300), memory for own name (Early Negative Enhancement to Sound of Own Name); and comprehension (N400). The 5-minute auditory stimulus sequence was comprised of tones (2.5 minutes) followed by speech (2.5 minutes). Amplitude and latency data were collected on all components. For the purpose of a comparison across clinical tests, the current study focused specifically on presence or absence of N100 (sensation) and P300 latency, a well-established ERP measure of information processing. Other ERP component measures are being analyzed, and the results will be detailed in future publications. In the present study, after screening for an N100 response, patient P300 latencies were compared to those of 100 healthy normative controls and then correlated with patients' clinical scores on the GCS, CRS-R, and FIM (selected cases).

5.3.6 Data Analysis

In order to address challenges related to POC clinical testing in severe brain injury, the EEG analysis involved advanced methods to ensure proper identification of the P300 latency. Data analysis was performed using a combination of BrainVision Analyzer 2 (Brain Products GmbH, Germany) and custom software in MATLAB (MathWorks, USA). Raw continuous EEG data were band-pass filtered to 0.1-20Hz, then visually inspected to reject segments containing artifacts. Temporal independent component analysis (ICA) was performed for blink detection, followed by ocular correction using the Gratton and Coles method (Gratton, Coles, & Donchin, 1983). Subsequent pre-processing was carried out according to established methods (Luck, 2014), comprised of band-pass filtering (0.1-10Hz), segmentation (-100 to 900ms) of epochs, baseline correction (-100 to 0 ms), and conditional averaging. To further enhance the signal-to-noise ratio and optimize component detection for a heterogeneous patient sample and various clinical sites, segmented data were processed using wavelet filtering prior to trial averaging to obtain ERPs (Daubechies, 1990). In usual ERP practice, across-trial averaging is often employed to enhance the signal-to-noise ratio to isolate event-related brain potentials that are often several magnitudes smaller than background EEG. However, these often require a large number of trials, which is impractical within a clinical setting where signal-to-noise is suboptimal. Accordingly, we utilized a recently developed alternate signal to noise ratio enhancing approach using wavelet filtering. The wavelet method is well-suited to non-stationary ERP analysis (Demiralp, Yordanova, Kolev, Ademoglu, Devrim, & Samar, 1999). The wavelet filtering technique builds upon previous literature (Hu, Mouraux, Hu, & Iannetti, 2010) and uses the sample of 100 healthy control ERP data to derive thresholds for filtering patient data. Specifically, continuous wavelet transform (CWT) was first applied to the grand-average ERP waveform of the healthy control data as follows:

$$X(t,f) = \int_{\tau} x(t) \cdot \sqrt{\frac{f}{f_0}} \cdot \psi^{*}\left(\frac{f}{f_0} \cdot (\tau - t)\right) d\tau$$

$$\psi(t) = \frac{1}{\sqrt{\Pi f_b}}\, e^{2i\pi f_0 x}\, e^{\frac{-x^2}{f_b}}$$

where $x(t)$ is the original grand-average ERP signal in time domain, $X(t,f)$ is the transformed signal in time-frequency domain, $\psi(t)$ is the mother wavelet in the form of a complex Morlet function with central frequency f_0, and t and f are the time and frequency indices, respectively. The parameters f_b and f_0 were set to 0.05 and 6, respectively, in accordance with previous literature (Hu et al., 2010).

The power spectrum was computed from the transformed time-frequency signal as the square of the magnitude of the wavelet coefficients, and was baseline corrected by subtracting the mean of the spectral power during the 100ms pre-stimulus interval. The power spectrum was then normalized, and the cumulative distribution function (CDF) computed. The dynamic range of the CDF was thereafter derived, and the filtering threshold was determined as the wavelet coefficient corresponding to 85th percentile of the CDF. Subsequently CWT was computed for single trial data for each patient, and all resulting wavelet coefficients below the threshold level were set to zero. The filtered trial-level spectra were then converted back to time domain via inverse continuous wavelet transform (iCWT) as below:

$$y(t) = C_{\psi} \int_{\tau} \int_{f} X'(t,f) \cdot \sqrt{\frac{f}{f_0}} \cdot \psi\left(\frac{f}{f_0}(t - \tau)\right) \cdot \left(\frac{f}{f_0}\right)^{2} d\tau\, df$$

where $y(t)$ is the converted signal in time domain, $X'(t,f)$ is the wavelet transform after filtering, C_ψ is a scalar normalization coefficient, and other quantities are defined as previously illustrated. Finally, the wavelet-filtered trial-level data for each patient were averaged to derive the ERP waveform for that patient. Although CWT preserves non-phase-locked information, the application of iCWT prior to conditional trial-averaging for ERP generation ensures that the final waveforms contain only responses that are both time- and phase-locked, in line with traditional ERP practice (Luck, 2014).

Both healthy control and patient data were subjected to wavelet filtering prior to ERP derivation and the same filtering thresholds were used in both healthy control and patient data. The results reported herein thus focused on relative differences between the two groups rather than raw numerical values. The current study focused on evaluation of P300 latencies only and did not compare P300 amplitudes between the healthy and patient groups because the wavelet filtering method is known to reduce ERP amplitudes but does not significantly impact component latencies (Hu et al., 2010). Statistical significance was evaluated between the control and patient groups using Welch’s t-test. In order to determine whether differences in outcomes existed between TBI and n-TBI populations, the TBI sub-group was also compared to other patients and healthy controls (corrected for multiple comparisons).

Further statistical analyses were performed to evaluate the effect of unequal subject numbers between the control and patient groups. This involved randomly selecting a sub-group of healthy control participants equal in number to that of the patient group, and repeating the Welch’s t-test. This process was repeated 10 000 times following randomized sub-group selections, and the mean probabilities were computed.

Patient ERP results were excluded if there was no clear N100 response to the tones. Two separate groups of blinded examiners (RCND, SGH, CL versus BD, CfP) reviewed the data to identify presence or absence of the N100 and P300 responses. Inter-rater reliability for the P300 was 95% (19/20) for averaged responses. However, when the individual (versus averaged) waveforms were evaluated for the patient (Participant 19), concordance was reached.

5.4 Results

Figure 2a shows the correlation between the GCS and CRS-R scores for all 28 patients (*r* = .937, p<.01). Figure 2b demonstrates the correlation (.933) is significant (p<.01) specifically for the TBI only group (n=12). Figure 3 shows a representative P300 response for a healthy control and a patient participant.

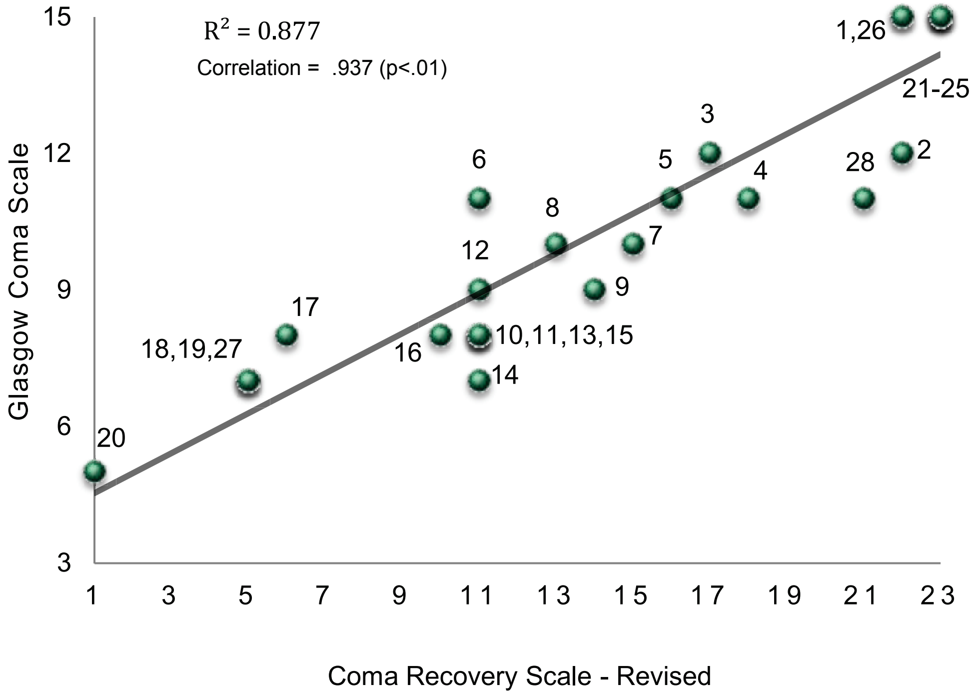

Figure 2a: GCS – CRS-R Correlation – All Participants

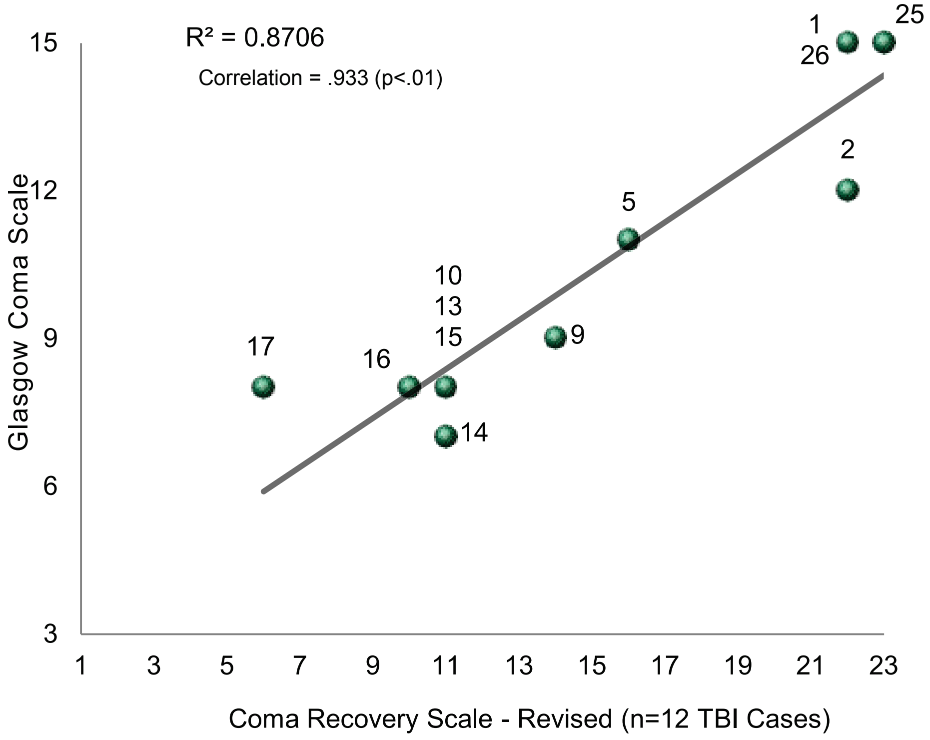

Figure 2b GCS – CRS-R Correlation – TBI Participants Only

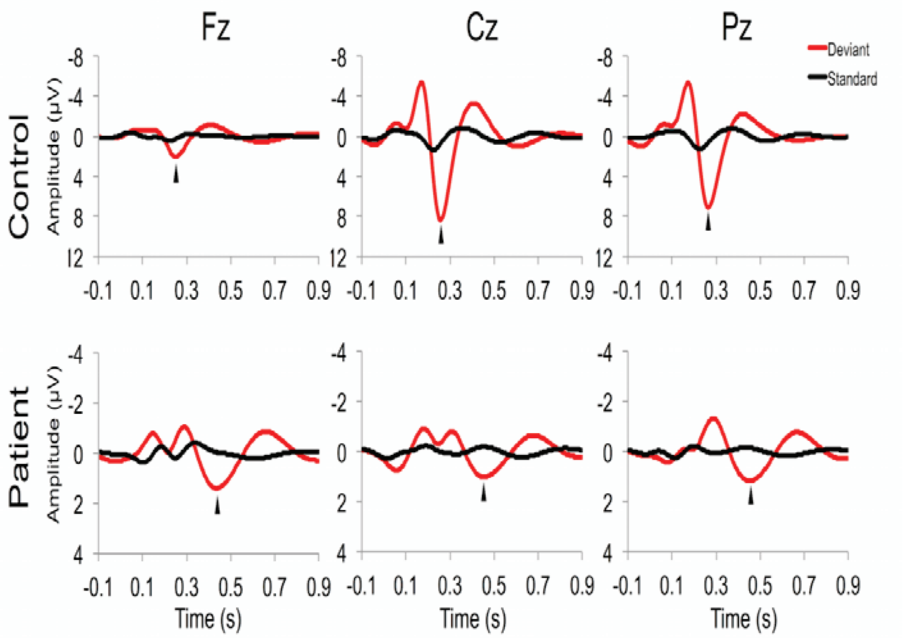

Figure 3: Sample P300 Waveforms from Control and Patient

In keeping with previous work (Chennu et al., 2013; Linden, 2005; Picton, 1992; Perrin et al., 2005) patients in this study with severe stroke and brain injury (n=20) showed delayed P300 latencies compared to those of the 100 healthy controls ($p<0.05$) (Sculthorpe-Petley et al., 2015). Participant 8, who was partially/inconsistently responsive, did not show a P300 response so the averages were based on 19 individuals. The mean P300 latency for patients (n = 19) was 368 ms (SD = 82 ms), whereas the mean P300 latency for 100 healthy controls was 282 ms (SD = 42ms). This result was not affected by the unequal subject numbers between the two groups, as statistical significance was maintained even when an equal number of control participants were randomly selected from the 100 overall control population and compared to patients ($p<0.05$). Bootstrapping confidence interval (CI) analysis was performed by randomly selecting a subsample of 10 participants from each of the healthy and patient groups, and computing the group means from the subsample. Significance remained when this was repeated 10 000 times. The graphic corresponding to the permutation statistic is included as supplemental material (Figure SM1). Figure 4a is a box plot showing the mean P300 latencies (+/- SD) for the healthy (N=100) and patient (N=19) groups, with individual data points overlaid. As shown in Figure 4b, the group means were 282.1 +/- 41.6 ms for healthy controls, 367.2 +/- 86.9 ms for TBI and 368.8 +/- 81.8 ms for n-TBI including stroke. The TBI and n-TBI/stroke groups' mean P300 latencies were not significantly different from each other. All groups were compared to each other with two tailed 2-sample unequal variance t-tests, with the TBI and n-TBI groups found to be significantly different from healthy controls ($p<0.05$, Bonferroni corrected). Figure 4c details the P300 latency of each patient with severe brain injury (TBI or n-TBI) or stroke. Participant 8, who was partially responsive, did not demonstrate a P300 response despite an intact N100 and some behavioural signs of hearing (e.g. startle response to out of sight noise). This demonstrates an important proviso for the HCS and ERPs in general: while positive HCS results have the potential to provide informative data - a negative result such as obtained from Participant 8 (clearly partially responsive) must be treated as an unknown rather than as an indication of absence of awareness. The box plots in Figure 4d show the distribution of P300 latencies in each group, including healthy (N=100), fully conscious

(N=5), partially conscious (N=10), non-responsive (N=3), and comatose (N=1) with individual data points specified.

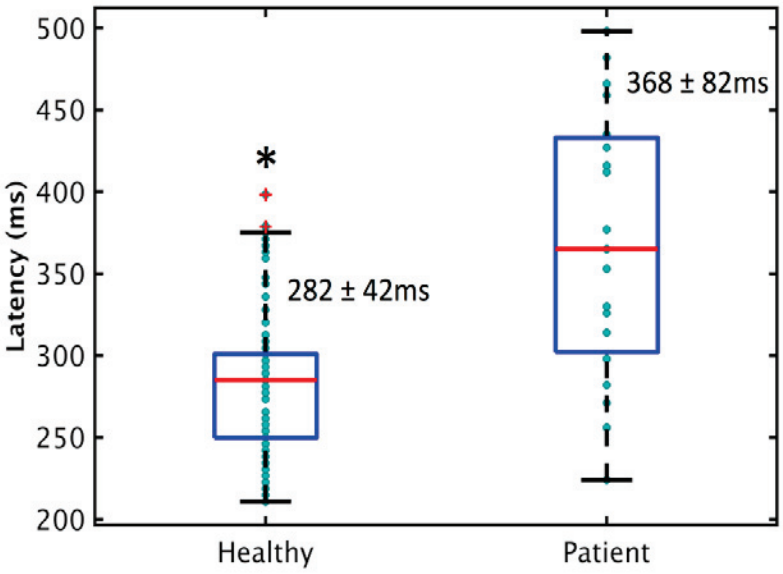

Figure 4a: P300 Latencies for Healthy and Patient Groups with Data Points

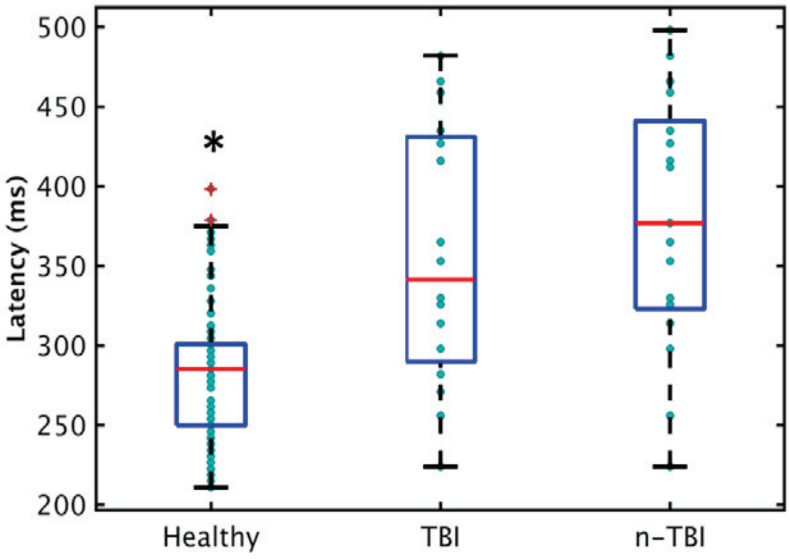

Figure 4b: P300 Latency in TBI/Stroke and Healthy Control Groups with Data Points

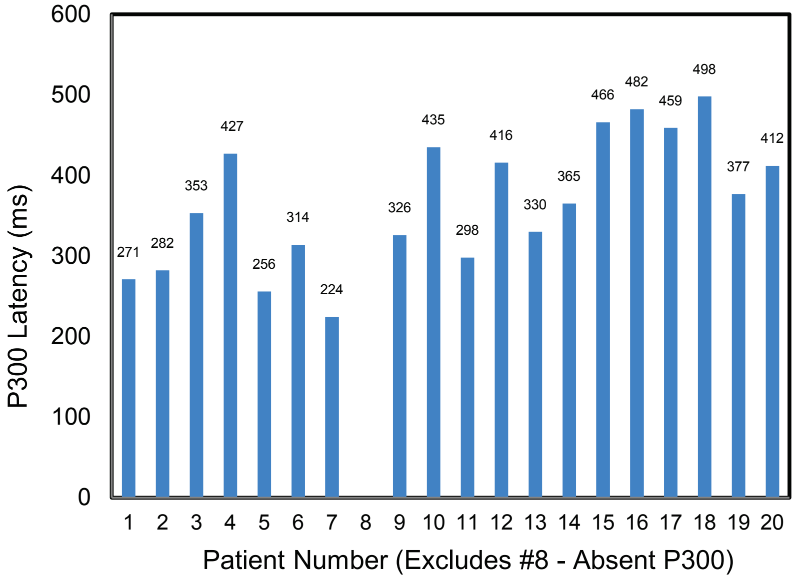

Figure 4c: Patient P300 Latencies in Milliseconds

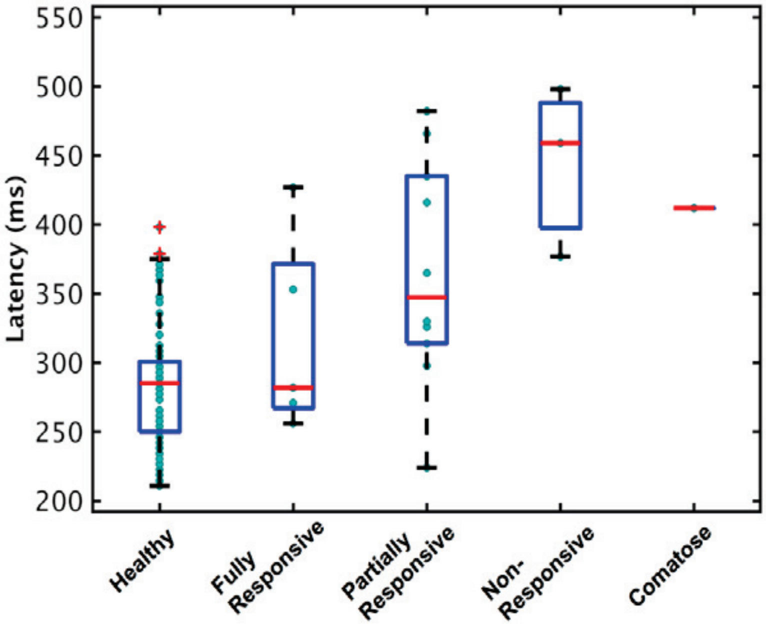

Figure 4d: P300 Latency Distribution in Healthy Group & Each Severity of Patient Group

Two-tailed bivariate Pearson correlations demonstrated that the P300 latency correlated significantly with the GCS (n=19, r= -.56, p<0.01), CRS-R Total Score (n=19, *r* = -.58, p<0.01), and FIM score (n=7, *r* = -.74, p<0.05, 1-tail). See Figures 5a-c.

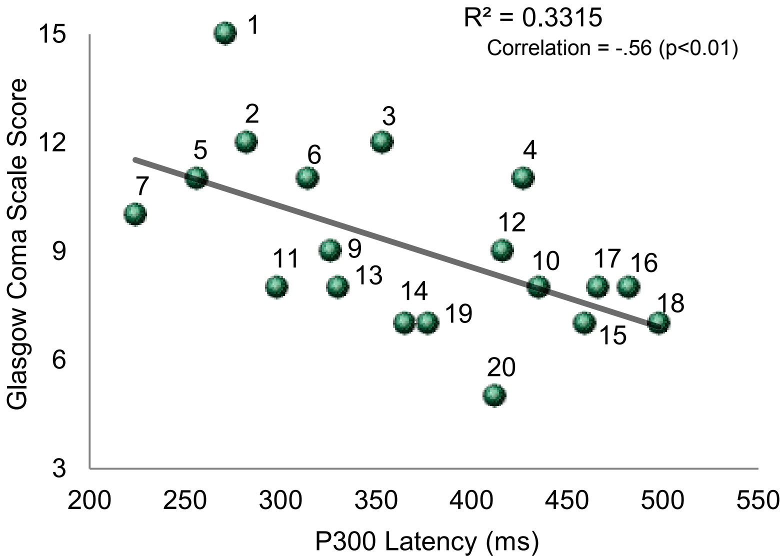

Figure 5a: GCS Score – P300 Latency Correlation

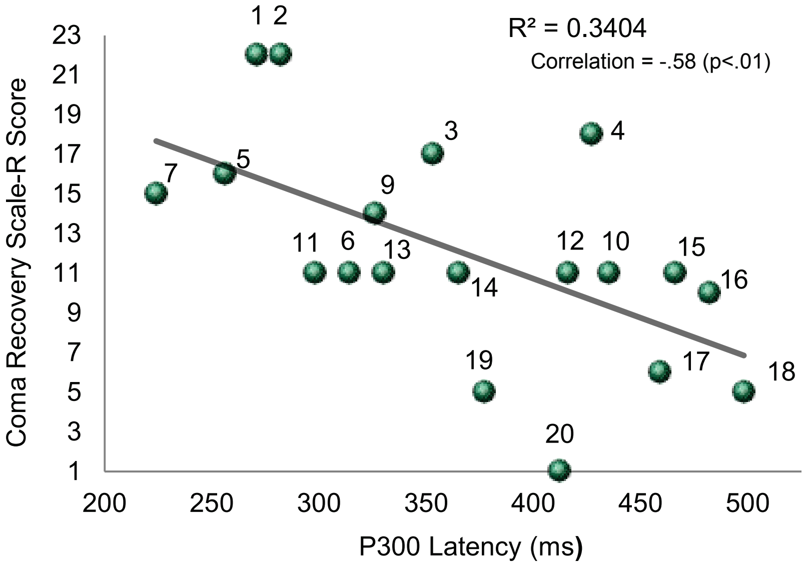

Figure 5b: CRS-R Score – P300 Latency Correlation

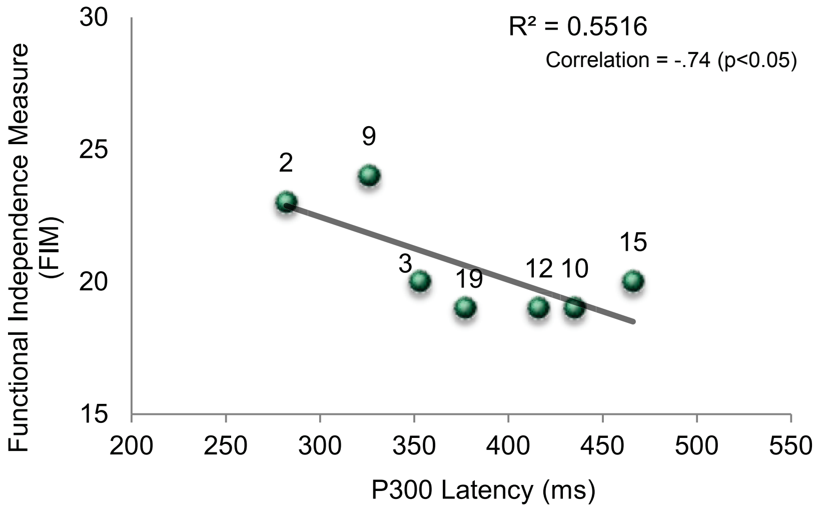

Figure 5c: FIM Score – P300 Latency Correlation

When only the TBI sub-group was considered, the P300 latency continued to correlate negatively with all clinical scores (p<.01) on 2-tailed tests except for the FIM (*r*=-.88), which did not reach significance. However, given FIM scores were not attainable for all TBI participants (n=4), this result is likely compromised by reduced statistical power. See Figures 6a-c.

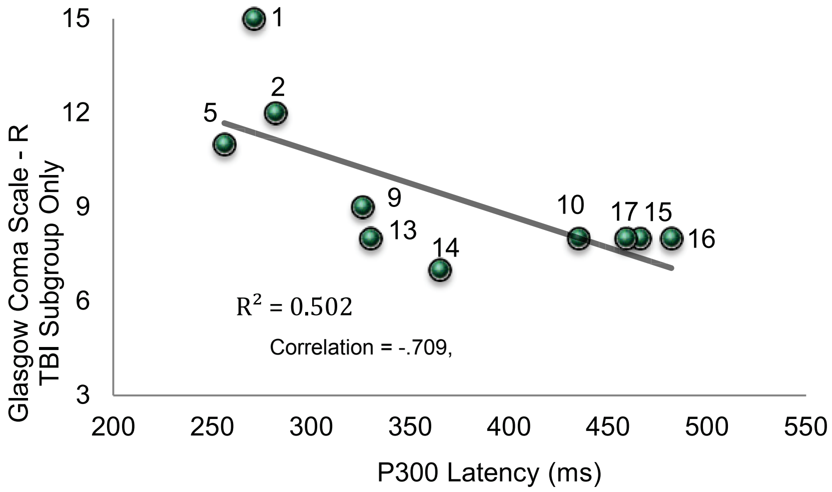

Figure 6a: GCS Score – P300 Correlation for TBI Group

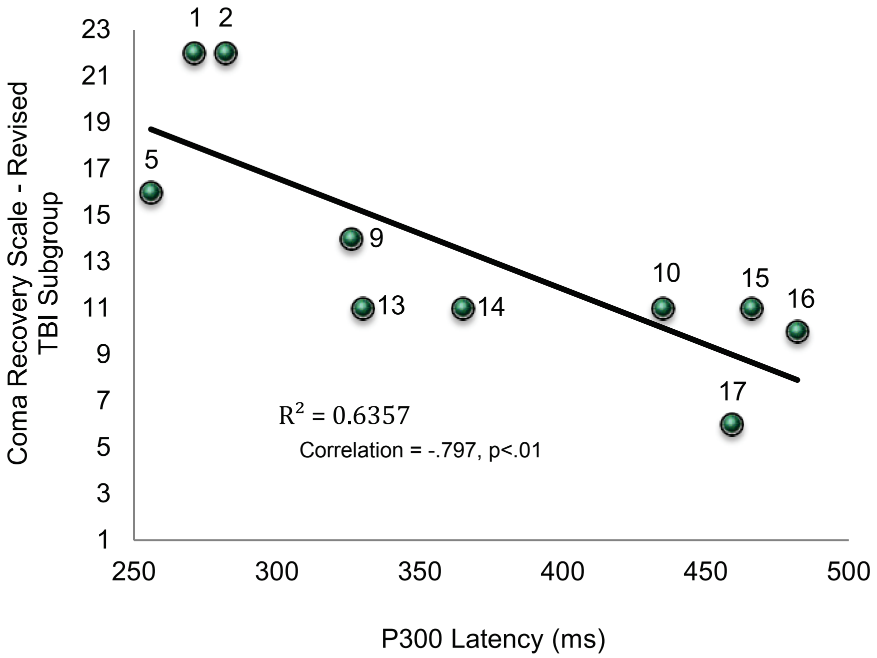

Figure 6b: CRS-R Score – P300 Correlation for TBI Group

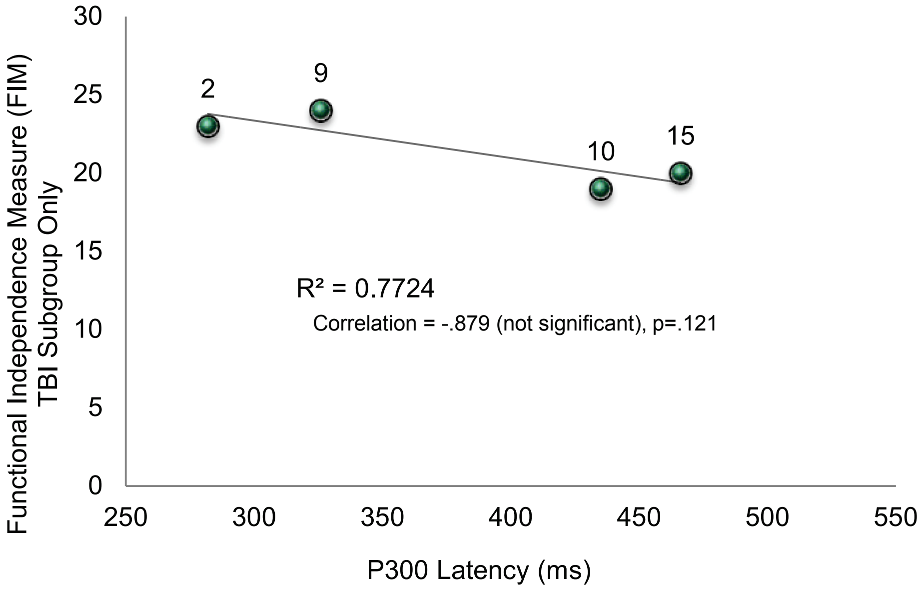

Figure 6c: FIM Score – P300 Correlation for TBI Group

5.5 Discussion

The primary objectives of this study were to examine the feasibility of using the HCS for POC evaluation in sub-acute settings nationwide in Canada. The findings demonstrated that HCS testing at POC is feasible in sub-acute settings, with patient P300 latencies significantly delayed relative to normative health control P300 latencies (Hypothesis 1). As expected, significant correlations were established across clinical measures (Hypothesis 2). Importantly, further correlational analyses showed significant linear relationships between individual patient P300 latencies and established clinical measures (Hypothesis 3). Bootstrapping confidence intervals for P300 latencies were calculated within both healthy and patient samples, and confidence intervals did not overlap between the healthy and patient samples. This result confirmed that it is possible to obtain objective brain measures in front-line, subacute POC assessment and monitoring applications – even in patients with severe movement impairments. However, HCS utility and diagnostic accuracy in early diagnosis remain unknown at this time.

In an important study, Chennu and colleagues (2013) demonstrated the P300 marker of attention (exogenous and/or endogenous) in some behaviourally unresponsive patients. The authors evaluated P3a and P3b in 30 patients and 8 healthy volunteers. Nine subjects were rejected due to heavy artefact noise. In the 21 remaining patients the authors showed evidence of exogenous and endogenous attention in a patient in an unresponsive wakeful state and exogenous attention in three patients in minimally conscious states. The unresponsive patient and two of the three minimally conscious patients subsequently demonstrated command following during tennis imagery tasks on fMRI. Whereas the focus of the aforementioned study was to determine the presence or absence of the P300 family of responses in the specified time window, this HCS study evaluated the correlation between behavioural scales and P300 latency. Like in the auditory HCS study, Chennu reported a high level of inconsistency in the responses across the patient group. Kouchoubey and Pavlov (2018) completed a systematic review and meta-analysis of the relationship between brain data and outcome in DoC including 47 publications. Surprisingly, their results demonstrated that P300 and fMRI showed poor prognostic effects. This however, does not negate the importance of the measures in understanding the nature of a patient's condition. While it is clear that P300 latency allows us to make assumptions about information processing, other ERP measures such as N400, may be more useful for prognostication. Related studies by our group (Hajra et al., 2018; Pawlowski, 2018) and others (Steppacher et al., 2013) explored the potential of using N400 as a physiological indicator of masked conscious awareness with promising results.

Clinical settings have not capitalized on the potential of electrophysiology to contribute to the process of DoC evaluation, status monitoring, and care planning/service designation. There is a pressing need for an easily deployed, low-cost, non-invasive, and repeatable objective assessment strategy that can be used to serially monitor conscious awareness at the single patient level. Given that a patient's state of conscious awareness hinges on many factors and can change over time; it makes sense to assess and monitor these patients once they are medically stable in the sub-acute phase. In recent years, several measures for capturing task related neural activity such as alpha band power, spectral edge frequency, and mean spectral frequency have been identified (Bia, Xia, & Li, 2017; Song, Zhang, Cui, Yang, & Jiang, 2018). Additional measures have also been reported for evaluating blink related oscillation effects, with some demonstrated efficacy in differentiating between vegetative and minimally conscious state patients (Bonfiglio et al., 2013; Bonfiglio et al., 2014; Liu, Ghosh Hajra, Cheung, Song & D'Arcy, 2017). As an important first step, André-Obadia and colleagues (2018) have proposed recommendations for electroencephalography and evoked potentials in comatose patients. Future work will also explore spectral markers derived from HCS data to further characterize the rich data available and this may yield complementary information. It may also be useful to explore the utility of the device in acute settings, although in acute settings many factors (consciousness-altering drugs, coexisting medical problems, etc.) can reduce the feasibility of the test and compromise the validity of the results.

The HCS uses a portable EEG system to rapidly deliver a compressed ERP sequence at POC without interrupting daily clinical routines or exhausting the patient. Given that this system does not rely on overt responses, it can be done independent of behavioural responses and therefore is not confounded by 'motor-mind disconnection'. It is imperative that patients in minimally conscious or locked-in states receive the stimulation and rehabilitation necessary to maximize their odds of improvement (Giacino, 2004; Illman & Crawford, 2017; Fins et al., 2016).

The current study has a number of caveats. Given the relative rarity of disorders of conscious awareness and challenges inherent to fluctuating health status, securing an adequate sample size was challenging. This is especially the case when the objective is to evaluate a deployable HCS across a wide array of settings. Nonetheless, similar studies have employed a wide range of sample sizes ranging from N=8 (Bekinschtein, Dehaene, Rohaut, Tadel, Cohen, & Naccache, 2009) to N=173 (Sitt et al., 2014). Several studies targeting the P300 family of responses (Ragazzoni et al., 2013; Chennu et al., 2013; Cavinato et al., 2011) have used sample sizes similar to the present study.

Another caveat relates to selection bias. In this study, patients were referred by caregivers or therapists who likely preferentially referred patients suspected to have some degree of awareness. Given this bias, separate validation studies would be required for patients with absolutely no clinical or behavioural indicators of consciousness. Further work is required to model effects across different centres to better understand key influencing factors (e.g., hardware, environment, data collection protocols, et cetera).

Due to the nature of conscious awareness, studies of DoC also face inherent challenges of sensitivity and specificity. Diagnosis occurs at the individual patient level so although showing group differences is necessary for a tool to be diagnostically useful, it is not sufficient. However, because a 'gold standard' for the assessment of consciousness independent of behaviour does not exist, it is very difficult to validate a new tool. Further, as is the case with other technologies that have been trialed for diagnosing conscious awareness such as fMRI, the HCS is sensitive to specific markers like the P300 but lacks specificity in the event of negative results. Therefore, negative test results must be considered inconclusive. Even though ERPs can eliminate reliance on overt responses, participation requires basic attention, sensory, perceptual, and often, receptive language capacity. A breakdown can occur at the input stage, even if internal awareness exists. In order to mitigate this confound, a larger, multi-sensory diagnostic battery is necessary.

Author Contributions

Conceptualization and study design: SGH, CL, DW, CfP and RCND. Literature research: CfP, SGH, CL, and RCND; Data collection: CfP, SGH and RCND; Analysis planning: SGH, CL, CfP and RCND; Data analysis: SGH, CL, CfP, BD, SG, and RCND; Results presentation: CfP, SGH, CL, and RCND; Analysis outcome verification: SGH, CL, and RCND; Results interpretation: All authors; Manuscript interpretation: All authors; Critical editing and approval of submission: All authors.

Conflicts of Interest and Sources of Funding

While associated with the National Research Council of Canada, D'Arcy, R.C.N., Weaver, D., Ghosh Hajra, S., & Liu, C. C. were inventors on the patent describing the intellectual property for the Halifax Consciousness Scanner, which is wholly owned by the Crown (USA patent # 13701252, European patent # 2011797433, international PCT application number CA2011050367). This may qualify them to receive a small percentage of royalties from the Government of Canada. Ghosh Hajra, S. was supported by the Multi-Year Funding scholarship from Simon Fraser University and Liu, C.C. holds a scholarship from the Canadian Institutes for Health Research (CIHR, Grant # GSD-140381). D'Arcy, R.C.N. is President and Chief Scientific Officer of HealthTech Connex, which may qualify him to receive benefit from commercialization of work related to this research. No conflict of interest or sources of funding were declared for the remaining authors.

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Supplemental Material

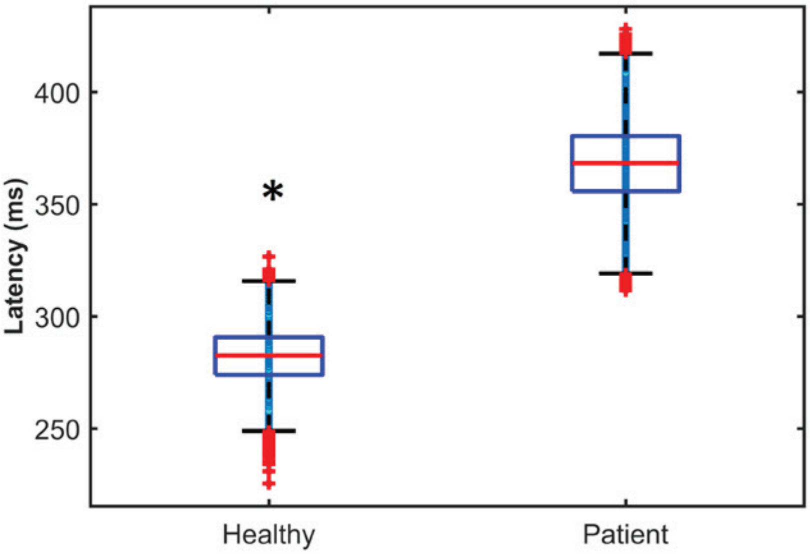

Figure 5SM: Boxplots Showing the Distribution of the Group Means for Healthy and Patient Groups

Supplemental figure shows boxplots showing the distribution of the group means for healthy and patient groups. A multi-sample bootstrapping approach was utilized in which each iteration involved the random selection of a subset of 10 individuals in each of the healthy and patient groups, and the box plots denote the group means across 10,000 bootstrapped permutations. Blue boxes denote quartile ranges, red line denotes median. Individual group mean data points are shown in cyan, while red crosses denote outlier values more than 1.5 times away from the nearest quartile boundary. *p<0.05 between groups.

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Chapter 6 (Manuscript 2)

Visual P300 to familiar & unfamiliar faces & places: A portable EEG validation study

Carolyn M. Fleck-Prediger[1,2*], Bruce D. Dick[1,3], Caressa C. Liu[4,5], Sujoy Ghosh Hajra[4,5], Jonathan W.P. Kusiak[1,6], Abdel Tayem[6], Mary Wilkinson[1], D. Shaun Gray[1,2,7], Esther Fujiwara[8], Ryan C. N. D'Arcy[4,5] & Kyle E. Mathewson[1,6]

[1]Neuroscience and Mental Health Institute, University of Alberta, Canada; [2]Halvar Jonson Centre for Brain Injury, Canada; [3]Departments of Anesthesiology & Pain Medicine, Psychiatry & Pediatrics, University of Alberta, Canada, [4]Faculty of Applied Sciences (Engineering Science and Computing Science), Simon Fraser University, Canada, [5]ImageTech Lab, Simon Fraser University and Fraser Health Authority, Canada, [6]Department of Psychology, University of Alberta, Canada, [7]Division of Physical Medicine and Rehabilitation, University of Alberta, [8]Department of Psychiatry, University of Alberta, Canada

*Correspondence address: Halvar Jonson Centre for Brain Injury Rehabilitation, Centennial Centre for Mental Health and Brain Injury, Ponoka, AB. Canada Tele: 403-783-7815; Fax: 403-783-7869; email: carolyn.fleck-prediger@ahs.ca

Visual P300 to familiar & unfamiliar faces & places: A portable EEG validation study

Abstract

Experiments using electroencephalography (EEG) are usually performed in controlled laboratory settings. However, to enable use in generalized clinical settings, new applications must take advantage of portable EEG devices. Accordingly, we used a portable EEG MUSE device to investigate processing differences between familiar and unfamiliar photographs. The study intent was to investigate differences in the P300 event-related potential (ERP) to familiar and unfamiliar photographs in healthy controls using a visual oddball paradigm. Familiar photographs (targets) evoked statistically significant P300 responses compared to unfamiliar photographs (standards). The MUSE device is portable and unobtrusive which makes this application feasible with patients who experience disorders of consciousness after neurological injury.

Keywords: Electroencephalography (EEG), Event Related Potential (ERP), P300, Brain Computer Interface (BCI), MUSE, Raspberry Pi.

6.1 Introduction:

Electroencephalography (EEG) has historically been restricted to controlled laboratory environments that limit applications at clinical point of care. However, the potential for clinical assessment using event related potentials (ERPs), which are derived from EEG, have been actively investigated since the early 1990s (Connolly and D'Arcy, 2000; Gawryluk et al., 2010; Gawryluk and D'Arcy, 2010). ERPs are time-locked to a particular event, often sensory stimulation, and are defined in terms of response polarity, latency, and topography (Gawryluk and D'Arcy, 2010; Kotchoubey, 2017). They have excellent temporal resolution (milliseconds) and reflect the time course of neural activity associated with sensory, perceptual, and cognitive processes (Hillyard & Anillo-Vento, 1998; Luck, 2000). ERPs are non-invasive, relatively inexpensive compared to other brain imaging methods, repeatable, and can quantify brain responses to stimulation without requiring an overt behavioral response, all of which makes them an attractive clinical tool.

Cognitive ERPs, such as the P300, reflect stimulus evaluation and information processing (Sur & Sinha, 2009). The P300 ERP can be elicited by an oddball paradigm in which two stimuli are presented in a random series, with one type (i.e. standard stimuli) occurring much more frequently than the other (i.e. target stimuli) (Jeon & Polich, 2001). In general, the more improbable the target stimuli, the higher the P300 response amplitude (Key, 2005). For most adults, the P300 latency range is 250-500 ms, but Polich (2007) specifies that this range can vary depending on variables such as stimulus modality, task conditions, and individual features such as age and health. Kutas & Federmeier (2011) specify that the latency can range from 250-800 ms, but others expand that upper range to 1000 ms (Duncan et al., 2009). The P300 response to visual stimuli occurs later than for auditory stimuli (Pawlowski, 2018) partially because the initial response time for stimuli by the primarily auditory cortex is 15 ms whereas for the primary visual cortex it is 40-60 ms (Picton, Stuss, Champagne, & Nelson, 1984). The P300 component has at least two dissociable parts, the P3a and P3b. Polich (2007) comments that the P3a originates from stimulus-driven task processing mechanisms, whereas the P3b originates from activity associated with attention and perhaps even subsequent memory processing. As part of the P300 complex, the late positive potential (LPP) is modulated by motivational significance and is enhanced to pleasant or unpleasant photographs compared to neutral photographs (Schupp, Cuthbert, Bradley, Cacioppo, Ito & Lang, 2000).

Gray and colleagues (2004) demonstrated that when healthy controls read their own name, versus other names, an augmented P300 response occurred approximately 500 ms after stimulus presentation. Similarly, for people with disorders of conscious awareness, self-referential stimuli such as the patient's own name (Fischer, Dailler & Morlet, 2008; Holeckova et al., 2006; Kempny et al., 2018; Perrin et al., 2006; Tacikowski & Nowicka, 2010) or own face (Tacikowski & Nowicka, 2010) are more likely to capture the person's attention. Given that personally relevant stimuli have the potential to augment the amplitude of the P300 response to targets, the present study on healthy controls used familiar and unfamiliar photographs and evaluated responses in the 400-600 ms latency range.

Traditionally, ERP experiments are performed in highly controlled laboratory settings to minimize background interference that can confound results (Van Hoey et al., 2000). In the present experiments, the commercially available MUSE brain sensing headband by InteraXon was used in combination with the Raspberry Pi 3 processor. Recently, Kuziek, Shienh, & Mathewson (2017) demonstrated that the small, battery powered Raspberry Pi 2 processor could be used to reliably administer an auditory oddball paradigm and highlighted the suitability of the Raspberry Pi 2 for testing in naturalistic environments. The MUSE-Raspberry Pi combination created a portable, cost effective, ecologically viable alternative to relying on a confining, difficult to apply EEG cap and large, stationary computer.

Two experiments were conducted to confirm the P300 response using the MUSE EEG. Experiment 1 used familiar and unfamiliar photographs to examine P300 response amplitude differences. Subsequently, Experiment 2 used conventional oddball stimuli (letter “O” vs letter “X”) to verify the P300 component. The hypothesis predicted that photographs of familiar faces and places would evoke larger P300 response amplitudes than unfamiliar photographs. The Raspberry Pi-MUSE set-up in combination with language- and literacy-free, self-relevant stimuli (i.e. familiar photographs) has potential applications in clinical patient care settings. For instance, strong electrophysiological responses to familiar faces or places may reflect an element of preserved covert awareness after severe brain injury when motor impairments negate intentional movement and speech.

6.2 Methods and Materials

6.2.1 Participants:

Health, demographic and handedness information was collected prior to the testing session. Table 1 provides the descriptive statistics for both experiments. All participants had normal or corrected to normal vision and no history of neurological problems. Participants refrained from using caffeine or other stimulants for at least three hours before testing. Written informed consent was obtained prior to the study, from the participant as well as from any friends and family of the participant who appeared in the submitted photographs. Participants were reimbursed at a rate of $20/h for their time. The experimental procedures were approved by the Human Research Ethics Board at the University of Alberta (Pro00044319).

Exps 1 & 2 Table 1: Demographics (Age, Sex, Handedness)

Experiment 1: (Photographs) N=15		
Males: N=6 (2 left handed)		
Females: N=9 (1 left handed)		
Mean Age (years)	Range (years)	Standard Deviation
22.1	18-31	+/-3.6
Experiment 2: (Letters) n=15		
Males: N=6 (2 left handed)		
Females: N=9 (1 left handed)		
Mean Age (years)	Range (years)	Standard Deviation
22.7	18-35	+/-5.5

Table shows demographics of participants including age, sex and handedness for Experiments 1 and 2.

6.2.2 Materials and Procedure

Experiment 1: In Experiment 1, participants submitted 5 photographs of their own face, 5 photographs of the faces of close family or friends, and 10 photographs of meaningful places (e.g. their living room, the front of their house, etc.). Sample photographs are shown in Figure 1a and 1b. The participants were instructed to submit color photographs that were sharp and free of text (e.g. no logos on shirts/hats etc.). The photographs could have been from the remote past (e.g. photographs from childhood) or from the recent past. For the photographs of people, the subject was to be facing-forward or nearly forward so both of his/her eyes were visible. To maintain consistent emotional valence, the people in the photographs were either to be smiling or have a neutral expression. The content was to be mainstream, without shocking elements. Photographs of faces in the foreground of a subtle background were permitted. Generic, easily recognizable places (such as a chain store) were excluded. The pictures were presented on a monitor with a black screen. The pictures were edited to 425 X 640 pixels for landscape-oriented photographs or 640 X 425 for portrait-oriented pictures and any text in the photo such as printing on a shirt was removed.

Figure 1a

Figure 1b

Exp 1 Figure 1a & b: Sample Photographs

Figure shows sample photographs of faces (1a) and places (1b).

The pictures were presented in an oddball paradigm that consisted of 80% standards (unfamiliar, impersonal pictures) and 20% target stimuli (familiar, personally relevant pictures). The photographs were repeated in 4 sets. In each set, 20 targets (personally relevant pictures) were viewed 3 times (60 views) and standards (unfamiliar photographs) were viewed 240 times. Short breaks were provided between sets. Therefore, a total of 300 pictures were viewed for 1500 ms each (total = 7.5 minutes) and a fixation cross was viewed for a 500 ms between each picture (total = 2.5 minutes). The inter-stimulus interval varied between 1000 and 1500 ms to limit entrainment effects by making the presentation of the stimuli less predictable. The participants pressed a button when they detected familiar photographs. In total, the experiment took less than 30 minutes.

Experiment 2: In Experiment 2, the participants engaged in a traditional oddball task using infrequently presented targets (letter O) amidst frequently presented standards (letter X), again with a 20:80 ratio of targets to standard stimuli. Participants were required to count the number of targets presented. They were not asked to press a button, as in clinical settings patients are often unable to press buttons on command. Each participant viewed the letter “O” 60 times and the letter “X” 240 times in 4 sets (100 views per set). Short breaks were provided between sets. In total, the experiment took less than 30 minutes.

6.2.3 Data Acquisition

The MUSE headset was used for all participants. For each participant, 10% of the nasion-inion distance, from the nasion, was used to determine where to place the front of the headband and 30% of this distance, from the inion, determined Pz. This helped to standardise electrode placement across participants. Prior to placing the electrodes, the selected face and scalp sites were cleaned and gently abraded. Conductive gel (Abralyt HiCl) was applied to all electrodes. Impedances were tested to ensure signal conduction and evaluate the amount of variability in the signal. If impedance exceeded 10 kΩ, the sensors were adjusted until impedance was minimized. Participants sat 57cm away from a backlit 1920 × 1080 pixel ViewPixx/EEG LED monitor refreshing at 120Hz in a well-lit, quiet room. The screen was centered in the participant's field of vision. In order to minimize noise and artefacts, participants were asked to relax, sit still, fixate on a cross in the centre of the screen, avoid patterned blinking and focus on the images or letters appearing on the screen without excessive gaze deviation.

The experiment was programmed and executed using Python. The experimental task was administered via the Raspberry Pi 3 portable computer. The Raspberry Pi was paired with the MUSE portable EEG system using MUSE LSL (https://github.com/alexandrebarachant/muse-lsl). Time series information for EEG data and stimulus streams were recorded using the open-source Lab Streaming Layer (LSL) application (MIT licensed). On the MUSE headset, electrode Fpz serves as the reference electrode and two ground electrodes straddle it. The MUSE uses seven sensors: two silver electrodes on the forehead (AF7, AF8); one behind each ear at the mastoid sites (TP9, TP10) constructed of conductive silicone-rubber; and three for reference. An additional auxiliary electrode was positioned at Pz and connected to the MUSE via the built-in Micro USB port to stream the data collected from that electrode. Data were recorded with a sampling rate of 256 Hz.

6.2.4 ERP Analysis

Custom Python scripts were created to present stimuli and collect the data for the experiment, while data processing and analyses were done with custom scripts in

MATLAB. Standard ERP analysis methods (filtering, artifact removal, and signal averaging) were applied to the EEG data (Luck et al., 2005). Data were re-referenced to linked mastoid (i.e., the average of TP9 and TP10 electrodes), and ocular contamination was corrected using adaptive filtering with AF8 as the ocular channel (He, Wilson & Russell, 2004). Data were then notch-filtered at 60 Hz (5kHz bandwidth), band-pass filtered to 1-10 Hz using a zero-phase 4th order Butterworth filter, and segmented into epochs (-200 to 1000 ms). Trials containing signals greater than +/- 100 microvolts were rejected, and data were then conditionally averaged to generate ERPs (Luck, 2014; Gawryluk & D'Arcy, 2010). ERP amplitudes in the target condition (i.e. familiar faces/places in Experiment 1, O's in Experiment 2) were derived by first locating the maximum amplitude within the 400-600ms interval in the target condition waveform, then computing the mean amplitude over a 20ms window spanning the maximum peak. The same 20ms window was then used for the standard condition to obtain its mean amplitude. Results were compared using paired t-test at the group level. The analysis was performed separately for the faces/places data (Experiment 1) and the "X" versus "O" data (Experiment 2). The P300 response was considered present if a positive maximal deflection was detected in the predefined timeframe (i.e. between 400-600 ms) within the target condition relative to the standard condition. This timeframe was selected in line with previous works (Liu, Ghosh Hajra, Cheung, Song & D'Arcy, 2017, Ghosh Hajra et. al. 2018, Pawlowski et. al. 2018), based on prior P300 literature, and given inspection of the grand-averaged waveform (Polich 2007, Pfabigan et al., 2014, Bennington and Polich 1999).

6.3 Results

Experiment 1: In Experiment 1, event-related potentials were successfully elicited for 13 of the 15 participants. Participants 04 and 11 were excluded due to data corruption and a recording error, respectively. As hypothesized, compared to the standard condition, significant P300 responses were recorded to infrequently presented target faces and places ($p<0.0001$, 2 tail) ($M = 3.95\ \mu V$; $SD = \pm 2.22$) (t stat = 7.27, 12 df) at the auxiliary Pz channel. Table 2 summarizes the target versus standard condition group amplitudes for photographs. Figures 2a and 2b show the ERP waveforms (2a) and boxplots illustrating the individual-level data distributions (2b) within the 400-600 ms latency range at the auxiliary Pz channel for familiar versus unfamiliar faces or places. Figure SM2c, available as supplemental material, shows bar graphs illustrating the amplitude difference between target and standard conditions for each participant. For familiar versus unfamiliar photographs, significance was maintained at Pz when 10 000 permutations were conducted to compensate for unequal sample sizes.

Exp 1 Table 2: P300 Amplitudes for Familiar vs Unfamiliar Photographs

Target Condition:	Amplitudes:	Standard Condition:	Amplitudes:
Familiar Photographs	3.95 ±2.22 µv	Unfamiliar Photographs	-0.87 ±1.12 µv
P Value (2 tails) for Target versus Standard Condition: p<0.0001			

Table shows mean group P300 amplitude for target conditions (all familiar photographs) and standard conditions (all unfamiliar photographs).

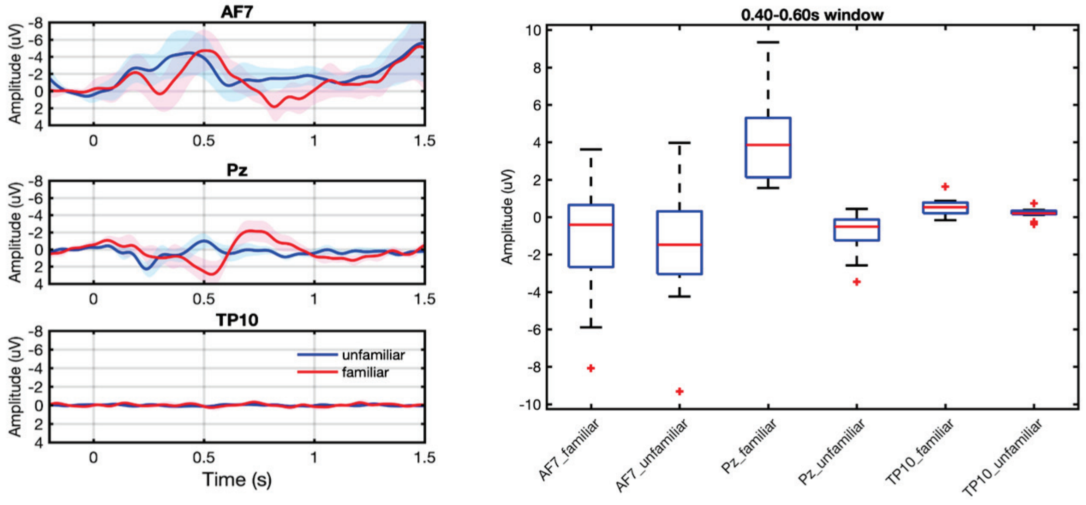

Figure 2a Figure 2b

Exp 1 Figures 2a & 2b: Waveforms & Box Plots of Mean P300 Amplitudes of All Familiar vs All Unfamiliar Photographs

Figure 2a shows waveforms illustrating the mean P300 amplitudes of all targets (familiar photographs, red line) versus all standards (unfamiliar photographs, blue line) between 400-600 ms at three sites (AF7, Aux and TP10) with shaded 95% confidence intervals. Figure 2b shows box plots of mean P300 amplitudes (+/- SD) illustrating the individual-level data distributions in response to all target versus all standards photographs between 400-600 ms in an oddball paradigm. Outliers specified by asterisks.

As summarized in Table 3, familiar faces, versus familiar places, evoked significantly greater amplitude P300 responses within the 400-600 ms latency range at the auxiliary Pz channel ($p<0.05$) (M = 4.59 µV; SD = ± 2.46 for faces versus 1.65 µV; SD = ± 3.29 for places) (t stat = 2.37, 12 df). Figures 3a and 3b show the ERP waveforms (3a) and boxplots illustrating the individual-level data distributions (3b) within the 400-600 ms latency range at the auxiliary Pz channel for familiar faces versus familiar places. Figure SM3c, available as supplemental material, shows bar graphs illustrating the amplitude difference between familiar faces and familiar places for each participant.

Exp 1 Table 3: P300 Amplitudes for Familiar Faces vs Places (p<0.05)

Condition:	Amplitudes:
Familiar Faces	4.59 ±2.46 µv
Familiar Places	1.65 ±3.29 µv

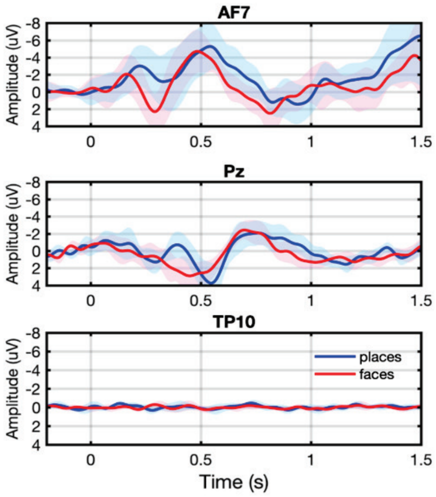

Figure 3a

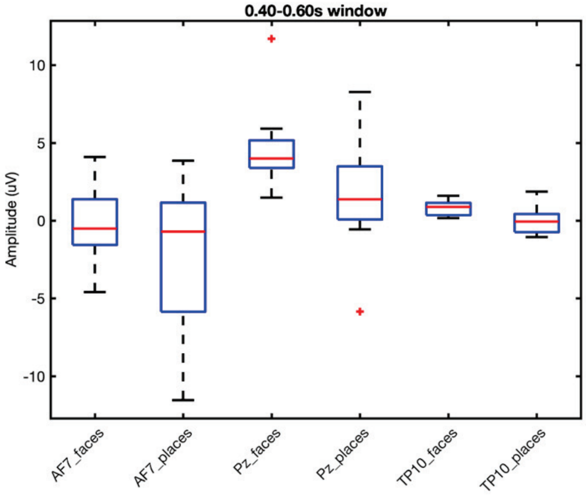

Figure 3b

Exp 1 Figure 3a & 3b: Waveforms & Boxplots of Mean P300 Amplitudes - Familiar Faces vs Familiar Places

Figure 3a shows waveforms illustrating the mean P300 amplitudes to photographs of familiar faces (red lines) versus familiar places (blue lines) between 400- 600 ms at three sites (AF7, Aux and TP10) with shaded 95% confidence intervals. Figure 3b shows boxplots of mean P300 amplitude (+/- SD) illustrating the individual-level data distributions in response to photographs of familiar faces versus familiar places between 400-600 ms in an oddball paradigm. Outliers specified by asterisks.

Experiment 2: In Experiment 2, ERPs were elicited in all 15 participants. As hypothesized, compared to the standard condition, significant P300 responses were recorded to infrequently presented letter “O” ($p<0.001$) (M=4.78 µV; SD = ± 3.22 µV) (t stat = 5.84, 14 df) at the auxiliary Pz channel. Table 4 summarizes the target (letter “O”) versus standard (letter “X”) mean group amplitudes. For the letter stimuli, significance at Pz was maintained at $p<.05$ when 10 000 permutations were completed to compensate for unequal sample sizes. Figures 4a and 4b summarize the event-related potential waveforms (4a) and boxplots illustrating the individual-level data distributions (4b) within the 400-600 ms latency range at the auxiliary Pz channel for letter stimuli. Figure SM4c, available as supplemental material, shows bar graphs illustrating the amplitude difference between targets (letter “O”s) and standards (letter “X”s) for each participant.

Exp 2 Table 4: P300 Mean Group Amplitudes for Letter “O” vs Letter “X”

Target Condition:	Amplitudes:	Standard Condition:	Amplitudes:
Letter “O”	4.78 ± 3.22 µv	Letter “X”	-0.05 ± 0.91 µv
P Value (2 tails) for Target versus Standard Condition: p<0.001			

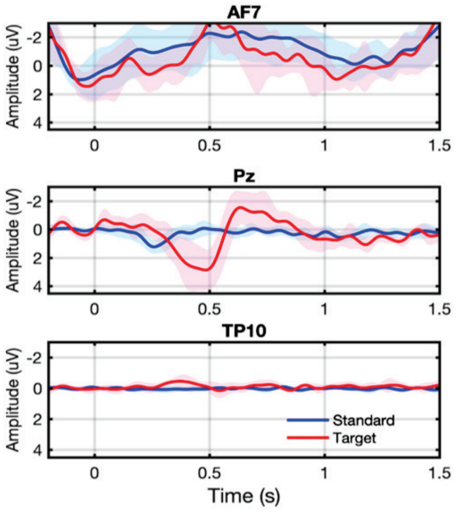

Figure 4a

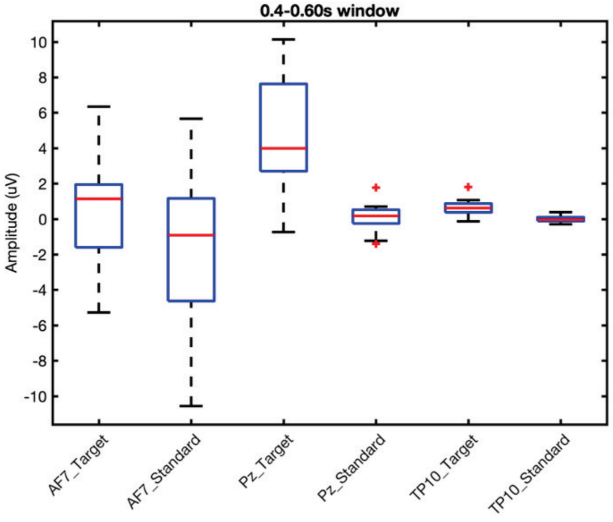

Figure 4b

Exp 2 Figure 4a & 4b: Waveforms & Box Plots of Mean P300 Amplitudes of Letter “O”s vs “X”s

Figure 4a shows waveforms illustrating the mean P300 amplitudes to the infrequently presented letter “O” targets (red lines) versus the frequently presented letter “X” standards (blue lines) between 400- 600 ms at three sites (AF7, Aux and TP10) with shaded 95% confidence intervals. Figure 4b shows box plots of mean P300 amplitude

(+/- SD) illustrating the individual-level data distributions in response to target letter "O"s versus standard letter "X"s between 400-600 ms in an oddball paradigm. Outliers specified by asterisks.

Comparison of Experiments 1 and 2: The mean group latency at the Pz (auxiliary channel) for the target conditions (familiar photographs and letter "Os") in Experiment 1 and 2 are specified in Table 5. The letter "O" P300 response occurred an average of 38 ms earlier than the combined faces and places targets. The target letter "O" in Experiment 2 evoked a greater amplitude P300 response than the combined faces and places targets in Experiment 1. However, the mean group amplitude of the familiar faces only (excluding familiar places) was comparable to the amplitudes evoked by the target letter "O". Based on verbal reports, participants consistently preferred the faces/places stimuli to the letter stimuli, often stating qualitatively that the "X" and "O" task was visually taxing and less interesting.

Exps 1 & 2 Table 5: P300 Mean Group Latency for Both Target Conditions

Target Condition:	Mean Group Latency:
Familiar Photographs	509 ± 0.06 ms
Letter "O"	471 ± 0.05 ms

Table contrasts the mean group P300 latency for target conditions (i.e. familiar photographs and the letter "O") in Experiments 1 and 2.

6.4 Discussion

The MUSE EEG findings supported the central hypothesis, which predicted that familiar faces and places would evoke significantly larger P300 responses than unfamiliar photographs (Experiment 1). The P300 was further validated by the standard oddball paradigm, in which infrequent target letters ("O") evoked significantly larger P300 responses. The P300 results also showed an interesting pattern across the different stimulus types that supported its known sensitivity to the salience of the eliciting stimulus, i.e. its reward value or affective significance (Keil et al. 2002, Yeung & Sanfey, 2004). When compared to the P300 from the standard oddball paradigm, the P300 amplitudes for combined faces and places were significantly smaller. However, there was no significant difference when the P300 amplitude to only familiar face stimuli was compared to the standard oddball P300. The standard oddball P300 response latency was also earlier than the P300 to faces and places. This is consistent with the relative differences in stimulus complexity impacting the latency of the P300 (Duncan et al., 2009). The P300 result suggested that familiar face stimuli were associated with greater target salience and may provide an important avenue for clinical applications with DoC patient evaluation.

In support of clinical translation, participants reported that they preferred viewing the photographs over viewing the letters. Participants unanimously self-reported that they found it difficult to maintain their focus and strained their eyes during the standard oddball paradigm; whereas they found the face and place stimuli interesting and engaging. Two of the 15 participants complained of a mild headache after the standard oddball session. It is noteworthy that these observations occurred even within a controlled laboratory setting. In clinical point-of-care settings, there are even more distractions and demands on attention. Further, patients with language or cognitive challenges or children may experience greater challenges sustaining their attention. The advantages of faces and places with embedded familiar targets, particularly when paired with the MUSE EEG, enable improved translation for P300 clinical applications.

The MUSE EEG with Raspberry Pi 3 was practical and effective as an experiment platform. The lightweight, commercially available, MUSE system was easily augmented with an auxiliary Pz electrode. The headset was easy to use and comfortable to wear. The total MUSE EEG application time was less than 5 minutes. Statistically significant differences were detected in two different experimental conditions (i.e. more complex faces/places stimuli and simple letter stimuli), suggesting the data quality was not compromised. However, as with other EEG systems, noise within the data did cause the omission of some participants' results suggesting continued sensor and data quality monitoring is important. In clinical applications, online monitoring of EEG quality may be necessary.

Kuziek, Shienh, & Mathewson (2016) reported that an auditory oddball task administered with the Raspberry Pi 2 produced similar ERPs to those derived from a desktop PC in a laboratory setting but indicated temporal differences and a slight increase in the number of trials needed for similar statistical power. Future studies may be completed to compare the performance of the Raspberry Pi 3 with a desktop system using a visual (versus auditory) oddball paradigm. In addition, it may be beneficial to trial the faces and places stimuli with a larger array of EEG electrodes (e.g. 16 or 32 channel). This would allow the data collected at the Pz site with the MUSE to be compared with results from another site such as Cz or with a combination of sites. The high-density study could be completed in combination with magnetoencephalography (MEG) to enable improved source localization (Ghosh Hajra et. al. 2018, Liu et. al. 2018).

6.5 Future Directions

In clinical situations, it is often difficult to know whether a patient is completely locked in, minimally conscious, or awake but totally unresponsive based on clinical behavioural measures such as the Coma Recovery Scale–Revised (Giacino, Kalmar & Whyte, 2004). There is value in assessing the patient's visual sensation, perception, attention, and ability to recognize familiar people and places. This information, albeit basic, is critically important to family members. It is also vital for treatment planning. If patients show physiological responsiveness to stimuli that are personally meaningful to them, it is feasible that brainwaves could be used to help them communicate in the absence of the ability to speak or move with intention. P300 based brain computer interface (BCI) is more feasible in patients who successfully demonstrate the basic cognitive and perceptual capacity for focused attention to a desired target.

Given the small sample size in this preliminary study, the next step is to test the stimuli on a larger number of participants. It would be optimal to establish an age specific visual P300 oddball normative reference dataset using familiar/unfamiliar photographs of faces and places. Initial clinical validation studies can then begin in parallel to better characterize the key factors required to optimize P300 assessment of familiar visual photographs at the point-of-care (e.g., Fleck-Prediger et al., 2014, Fleck-Prediger et al., 2018).

Conflicts of Interest and Sources of Funding

While associated with the National Research Council of Canada, D'Arcy, R.C.N., Ghosh Hajra, S., & Liu, C. C. were inventors on the patent describing the intellectual property for the Halifax Consciousness Scanner, which is wholly owned by the Crown (USA patent # 13701252, European patent # 2011797433, international PCT application number CA2011050367). This may qualify them to receive a small percentage of royalties from the Government of Canada. Ghosh Hajra, S. was supported by the Multi-Year Funding scholarship from Simon Fraser University and Liu, C.C. holds a scholarship from the Canadian Institutes for Health Research (CIHR, Grant # GSD-140381). D'Arcy, R.C.N. is President and Chief Scientific Officer of HealthTech Connex, which may qualify him to receive benefit from commercialization of work related to this research. No conflict of interest or sources of funding were declared for the remaining authors.

Author Contributions

Conceptualization and study design: CFP, RD, BD, DSG and KM. Literature search: CFP and MW. Data collection: CFP, MW, AT, JK, and KM. Analysis planning: CFP, RD, BD, KM, AT, JK, CL, SGH, and KM. Data analysis: CFP, RD, AT, JK, CL, and SH. Results Presentation: CFP, RD, BD, CL, SGH, and KM. Analysis outcome verification: CFP, CL, SGH, BD and RD. Results interpretation: CFP, RD, BD, KM, AT, JK, CL, SGH, EF and KM. Manuscript preparations: All Authors.

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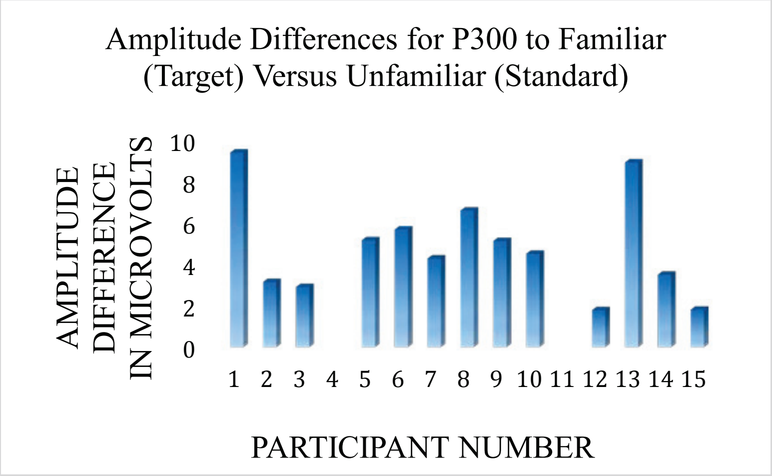
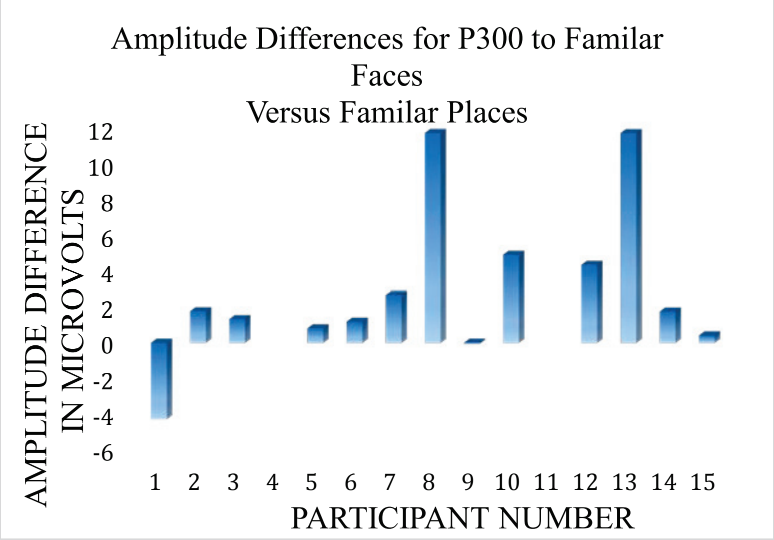
Supplemental Material



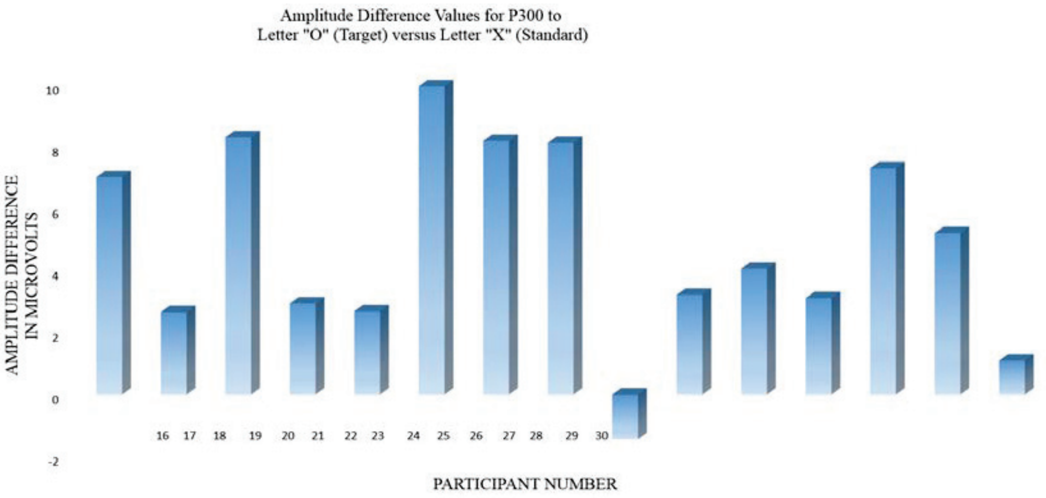
Exp 1 Figure SM2c: Bar Graph of Amplitude Differences between Target Photographs vs All Standard Photographs

Figure shows a bar graph of amplitude differences between all target (familiar photographs) and all standard (unfamiliar photographs) conditions between 400-600 ms in an oddball paradigm excluding participants 4 and 11.



Exp 1 Figure SM3c: Bar Graph of Amplitude Differences between Familiar Faces vs Familiar Places

Figure shows a bar graph of amplitude differences between photographs of familiar faces and familiar places between 400-600 ms in an oddball paradigm excluding participants 4 and 11.



Exp 2 Figure SM4c: Bar Graph of Amplitude Differences between Target Letter "O" vs Standard Letter "X"

Figure shows a bar graph of amplitude differences between target letter "O" and standard letter "X" for each participant.

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Chapter 7: Discussion

7.1 Contribution of Studies to DoC Research

There is an ever-growing body of literature pertaining to DoC and the assessment of DoC. Chapter 7 Figure 1 (Gosseries, Zasler, & Laureys, 2014) demonstrates the increasing number of publications regarding the subject in recent years. As detailed in the Introduction, (Chapter 1), DoC is a complex, multifaceted field of study. Researchers have used diverse and innovative tactics to tackle the challenges related to DoC prognosis, diagnosis and management. Despite advances, we are not yet able to accurately predict outcome, evaluate and monitor patient status, and differentiate between the various levels of consciousness.

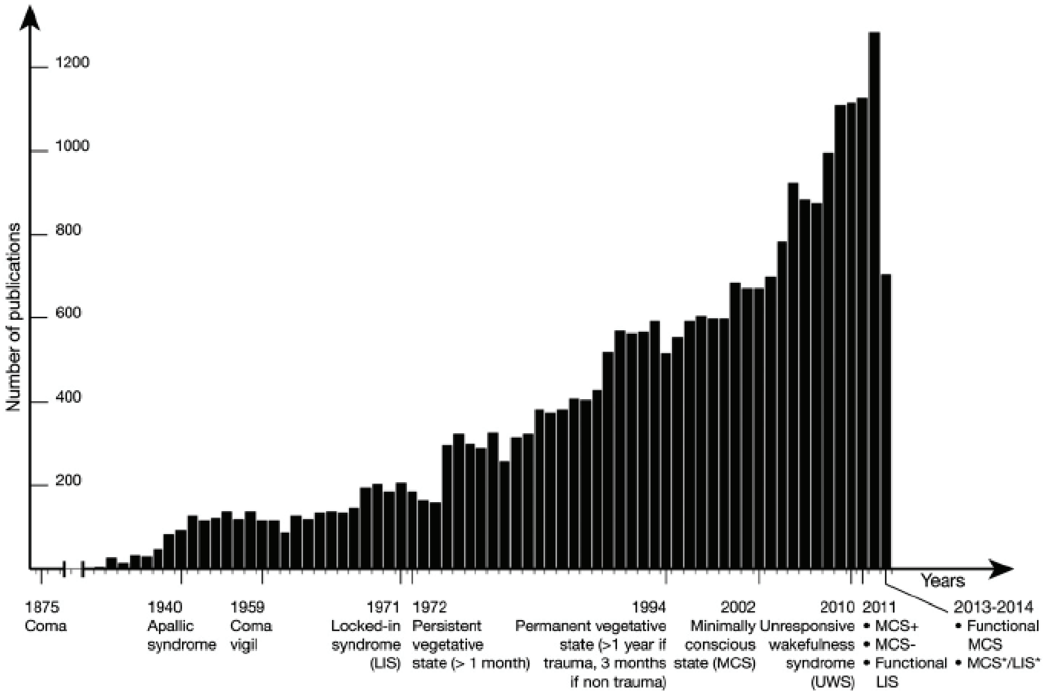

Figure 1: Number of Publications Regarding DoC

Figure by Gosseries, Zasler & Laureys (2014, p. 1142) reprinted with permission to demonstrate increasing number of publications regarding disorders of conscious awareness.

Diagnostically, the most daunting task is to differentiate unresponsive but wakeful patients from those who are either minimally conscious or completely locked in. Cognitive motor dissociation masks covert awareness in approximately 20% of patients who appear to be unresponsive. In order to best serve this patient group, cost effective, repeatable, valid and reliable diagnostic and monitoring systems must be available at point of care. Chapters 1, 2 and 7 highlight the work that has been done by clinically oriented research groups such as D'Arcy and colleagues, addressing this pressing need.

The literature review included here as Chapter 3 summarizes the work that has been completed in the field of evoked potentials and event related potentials for prognosis and differential diagnosis between unresponsive and minimally conscious patients. That literature review draws heavily on a recent systematic review by Hauger et al (2016) and a quantitative review by Kotchoubey (2017) which effectively summarized the contemporary state of the science. Adding to this, Chapters 1 and 3 discuss a comprehensive and systematic review update summary regarding DoC previously completed by Giacino and colleagues (2018). The literature review in Chapter 3 clearly demonstrates that although there has been significant progress, there is still much work to be done in the area of DoC. Chapter 3 also highlights the work of Kotchoubey and Pavlov (2018) who, after completing a thorough systematic review and meta-analysis of the relationship between brain data and outcome in DoC, have provided valuable recommendations to improve the quality, value and consistency of DoC research.

Chapter 4 (publication 2) describes a pilot study using the auditory version of the Halifax Consciousness Scanner (HCS) on a patient with severe traumatic brain injury (Fleck-Prediger et al., 2015). Importantly, this patient was pre-tested while unresponsive but awake and post-tested after intensive speech-language and dysphagia intervention. With intervention, the patient progressed from UWS to MCS+, as evidenced by (inconsistent) command following and many purposeful movements in contextually meaningful settings (e.g. some self-feeding). His P300 amplitude remained stable, while the amplitude of his N400 ERP response to semantically deviant sentences evolved in concert with his clinical progression. This early work further demonstrated the clinical utility and feasibility of the HCS and set the stage for a larger clinical trial. It also highlighted that multiple ERP measures may be more informative than single measures. This was proof of concept that electrophysiology can complement the rehabilitation process and provide an objective measure of change.

Chapter 5 (publication 3) describes national deployment of the HCS for trial with patients at point of care settings. The auditory HCS system was tested on 28 patients from various clinical settings. Building on a previous normative study of 100 healthy controls (Sculthorpe-Petley et al., 2015), this study enabled comparison of patient and neuro-typical HCS performance. Significant differences were apparent in P300 latency between healthy control and patient groups and among the fully responsive, partially responsive, and unresponsive patient groups. This study also allowed researchers to discover barriers to implementation and refine the evaluation process. The results from the auditory HCS system correlated with and extended behavioral measures including the Coma Recovery Scale-Revised and Glasgow Coma Scale. This study reinforced that in chronic phases, point of care testing is feasible and informative at the group level. Significant latency variability was apparent in the patient group reinforcing the concept that although group differences are compelling, at the single patient level, P300 latency is not sufficient for differential diagnosis. Additional research may prove that combined measures (e.g. P300 plus N400) may prove be more sensitive and specific. In addition, a multi-sensory, speech and language free approach may also be informative. Many patients could not be tested with the auditory version due to hearing impairment or language barriers. This reinforces the importance of multivariate analysis.

Chapter 6 (paper 4) describes a research project on 15 healthy controls testing language and literacy free, personalized stimuli (familiar faces and places) in a P300 oddball paradigm using the Raspberry Pi 3 for stimulus delivery/data collection and a MUSE headset for data collection. In this study, personalized stimuli, especially faces, evoked higher amplitude P300 responses than personally irrelevant photographs of faces and places. Further, personalized stimuli evoked higher amplitude ERPs than less engaging, impersonal stimuli (X standards versus 0 targets). In addition, when interviewed, participants consistently reported qualitatively that the generic (X versus 0) task was extremely boring, visually taxing, and exhausting whereas the photo task was engaging and even enjoyable. When asked which task they would be willing to do again, the participants unanimously chose the photo task. This is important in that patient engagement is an important factor in the validity of assessment results.

7.2 Limitations

The limitations of the studies described in this Dissertation are highlighted in each publication. In general, the biggest limitation regardless of the diagnostic strategy is translating group level differences to differential diagnosis at a single patient level. Until we overcome this barrier, we will not know what to make of each patient's individual results. Support Vector Machines (SVM) help make individual-level predictions, but more research is required in order to optimize this process. The second major limitation is the lack of a diagnostic 'gold standard' against which other tactics can be compared. It is difficult to evaluate the effectiveness of a new diagnostic tool when the only option is to compare the new tool to a measure known to be insensitive to cognitive motor dissociation (i.e. the CRS-R). The Halifax Consciousness Scanner, like all other assessment and diagnostic technology for DoC, is not yet an infallible diagnostic tool at the single patient level. Electrophysiology, while adding to the available tools, must be used in conjunction with other clinical and imaging tools. Even with the most rigorous and diverse combination of evaluations, it is still possible that people with cognitive motor dissociation will be under-diagnosed.

7.3 The Challenges in DoC Research

Research that involves patients with DoC is complicated, expensive, and time consuming with legal, ethical and humanitarian implications. Controversy surrounds 'right to die' versus 'right to live' movements and the latter has associated 'right to care and rehabilitation' dilemmas. Further, immense heterogeneity exists within the DoC category. In addition to etiology, people with DoC have different injury loci and severities and often have a host of diverse coexisting conditions. As well, premorbid factors such as age, education, experience, resilience, personality and sources of support vary from person to person. After injury, people have inconsistent access to medical interventions, rehabilitation, technology and care. Given the vast differences that can impact outcome, it is not surprising that we have difficulty anticipating how people will fare over the long term.

Despite the enormity of issue for individuals with DoC and their families, the condition remains relatively rare. Despite the challenges, there has been slow steady progress and convergent literature is beginning to hone research endeavors. Further, there is now overall agreement that differential diagnosis matters, as many decisions about life-preserving interventions and patient care are made based on diagnosis. A more favourable diagnosis (i.e. MCS or better) can be used to justify the opportunity for rehabilitation (Harrison & Connolly, 2013). Patients who are aware need to be streamed toward rehabilitation in order to minimize health complications such as contractors or pneumonia, manage pain issues, improve their communication, enhance their motor abilities, capitalize on technology and maximize the quality of their lives. Longitudinal studies also demonstrate that the outcome of severe brain injury may not always be as dire as medical personnel once thought. It is now clear that in some cases, improvement can be observed months and years after an injury. Sporadic cases of reawakening reinforce just how little we know about DoC and how much more work needs to be done on behalf of patients in this state.

7.4 Future Directions

Future directions are discussed at the conclusion of each publication. In sum, the next step for the auditory HCS study (Publication 2) is to evaluate the value of combining P300 and N400 results.

Regarding the visual version of the HCS, the logical next step is to trial the language and literacy free visual paradigm described in Chapter 6 on a larger sample of healthy controls using the HCS platform and/or the MUSE-Raspberry Pi 3 configuration. Magnetoencephalography (MEG) may even be useful to determine the nature and location of the event-related activation. There may also be value in evaluating the robustness of an N170 in response to faces as this could serve as an indicator of visual perception and processing. Although the N170 is not face-specific, it appears to reflect a degree of expert recognition. The type of picture (i.e. studio style verses body in subtle background) should also be parsed out. In order to evaluate integration of visual information, a pilot study involving incongruent scenes would complement the previously conducted auditory HCS word pairing and sentence tasks conducted by Pawlowski (2018). Once visual HCS norms for neurotypicals have been ascertained, patient trials like those completed with the auditory HCS could begin. It would be extremely useful to test a cohort of patients with both the auditory and visual versions of the HCS.

In order to further enhance the system, it could be beneficial to explore the possibility presenting photographs of people, places and personally meaningful objects in 3 dimensions through goggles to minimize environmental distractions. Adding an eye tracking component for evaluating visual patterns and areas of visual neglect or suppression also seems feasible and potentially beneficial, especially if this involved a form of audio feedback (e.g. hearing the name of the person when fixation occurs on a photo of self or a family member). Given that positive electromyography response to command may hold some value for differential diagnosis (Giacino et al., 2018) and is compatible with the HCS platform, there may also be value in combining the HCS and electromyography diagnostic techniques.

Recognizing a major barrier to effective clinical practice in a vulnerable patient sector, D’Arcy and colleagues set out to tackle the problem of point of care assessment and diagnosis is DoC. The subsequent series of inter-disciplinary research studies completed in relation to the Halifax Consciousness Scanner epitomizes strategic, robust collaborative, translational research. Although there are many future research tasks to complete and challenges to overcome, the potential of the HCS for assisting with DoC assessment, monitoring and rehabilitation streaming is exciting and readily apparent. This dissertation reviews the state of the science regarding early prognosis after severe neurological injury and diagnosis of DoC in acute and sub-acute settings. The research discussed herein expands the boundaries of science to promote clinically viable, multi-modal evaluations that are less confounded by language and motor limitations.

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