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EEG AS A DIAGNOSTIC TOOL IN ABI

TRINITY COLLEGE

ELECTROENCEPHALOGRAM AS A DIAGNOSTIC TOOL IN
ACQUIRED BRAIN INJURY

BY

MICHAEL ZARRA

A THESIS SUBMITTED TO
THE FACULTY OF THE NEUROSCIENCE PROGRAM
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EEG AS A DIAGNOSTIC TOOL IN ABI

Electroencephalogram as a diagnostic tool in acquired brain injury

By

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EEG AS A DIAGNOSTIC TOOL IN ABI

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Abstract

The ability of electroencephalogram (EEG) to be used as a diagnostic device for acquired brain injuries (ABI) has been conceptualized previously. Averaged event-related potentials (ERP) derived from an EEG are suitable as markers of dysfunction however, distinctive properties in the frequency domain have not been established previously. In the present study, we examined pre-existing EEG signal data of healthy adults (HA), mild ABI (mABI), and severe ABI (sABI) human groups. Through Fourier analysis performed in MATLAB, we found that individuals in our sample population (n=80) were able to be categorized into their respective group based on common neuronal activity detected at specific electrode locations. The characteristic activity patterns of individuals with ABI were found to be related to the amplitude of their theta waves. This novel way of interpreting EEG with respect to ABI, could significantly inform the diagnostic criteria for ABIs; it may also offer a pragmatic way for non-professionals to quickly detect concussions or similar injuries in competing athletes. Further efforts to sonify such neural activity of interest may elucidate more characteristic trends of ABI.

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Introduction

Background on EEG

Electroencephalography (EEG) is the measurement of brain electric fields via electrodes externally fixed on the head. EEG was introduced as a clinical tool by Hans Berger in 1929, and since then, EEG has become one of the most widely utilized neuroimaging techniques (Dyro, 1989). For the following discussion, the terms EEG and electrodes will refer to non-invasive external EEG and surface electrode, which do not require surgery.

Physiology of EEG signal

The EEG has been a powerful non-invasive brain imaging tool in neuroscientific research and the clinic (Cohen, 2017). What used to be like a fancy polygraph machine or a multichannel recorder generating inked lines on paper is now digitized. Despite the augmented technology, the output is very similar: several lines of waves varying in amplitude and duration (Dyro, 1989). The primary source of this EEG signal is generally agreed upon in what is known as the ‘standard model’: EEG signal arises as a result of synchronized synaptic activity in cortical neuron populations (Cohen, 2017; Jackson & Bolger, 2014). It is important to note that this model explains the existence of EEG but not the meaning of the content contained within the signal (Cohen, 2017). Neuroscientists typically distinguish between recording methods (e.g. EEG, electrocorticogram, and local field potential), but each measure refers to the same biophysical process (Buzasáki, Anastassiou, & Koch, 2012).

Most simply put, electrochemical signals passing from one neuron to the next create the electric fields measured by the EEG electrodes (Cohen, 2017). For example, the excitation of

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postsynaptic neurons results in extracellular voltage, which is more negative around the neural dendrites than along the rest of the neuron (Jackson & Bolger, 2014). This situation, when a region of negative charge is separated by a region of positive charge by some distance, is referred to as a dipole. The positively charged region is called the source while the negatively charged is called the sink (Buzasáki, Anastassiou, & Koch, 2012; Jackson & Bolger, 2014). Thus, every dipole has a negative and positive end and, therefore, will produce both a positive deflection and a negative deflection at different scalp regions resulting in different EEG signals at each region (Jackson & Bolger, 2014). The polarity of the signal measured at the scalp is also dependent on the orientation of the dipole. For example, if an excitatory postsynaptic potential arrives at the synapse of a cortical neuron, which is closer to the cell body rather than in the dendritic arbor, then the positively charged region would be closer to the scalp. Thus, an electrode will measure a positive deflection in voltage. If an inhibitory postsynaptic potential is closer to the cell body, then the opposite would occur, resulting in a negative deflection in voltage. Each postsynaptic potential would have the opposite effect if the dipole orientation was reversed. Thus, excitatory and inhibitory postsynaptic potentials can produce either a positive or negative deflection in the EEG signal depending on which charged region is closer to the scalp (Jackson & Bolger, 2014). An electrode is only capable of detecting dipoles when it is positioned relatively closer to one of the charged ends than the other, which allows for perpendicular tangential dipoles and parallel radial dipoles to be captured by EEG. If an electrode was equidistant from the source and the sink, then it would measure net neutral (Jackson & Bolger, 2014). It is important to note that the neural activity resulting in dipoles is not synonymous with an action potential. The voltage change of -70mV to 10mV that occurs when a neuron fires is an 'all-or-nothing' phenomenon, whereas synapse activity is not. Such activity can depolarize or hyperpolarize the synaptic membrane depending on the neurotransmitter

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released. It is also of shorter duration and involves changes on the order of a few millivolts (Dyro, 1989). In order for a dipole to be recorded with an electrode, the electrical signal must travel from the brain through the dura, the skull, the scalp, and finally to the electrode. The dipole of a single neuron is too small to be measured across that distance. Electrodes circumvent this challenge by detecting the sum of all the positive and negative charges within their vicinity. In other words, all the dipoles in the brain superimpose to yield an electric field at any given point in space, which is recorded by the relevant electrode (Buzasáki, Anastassiou, & Koch, 2012, Jackson & Bolger, 2014).

Normal or Variation of Normal EEG

Rhythms seen by EEG are classified by the number of cycles per second (i.e. frequency) in hertz (Hz). Delta rhythm is the slowest with a frequency of 0.5Hz to 4Hz, theta rhythm is between 4Hz and $7^{3/4}$ Hz, alpha rhythm is between 8Hz and 13Hz, beta rhythm is between 14Hz and 30Hz, and gamma rhythm is 30Hz to 100Hz (Dyro, 1989; Rapp, et al., 2015). A sigma rhythm of 14Hz to 15Hz is typical of sleep spindle activity; however, this activity is not present in the waking state. Brain activity during normal resting consists of only alpha rhythm in the posterior leads and beta rhythm in the anterior leads, whereas other rhythms are associated with sleep stages (Dyro, 1989). In the normal population, there are also variants that exist. For example, up to 10% of normal adults have no alpha activity, and instead their EEG consists of low-voltage activity of 13Hz to 30Hz (Dyro, 1989).

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Criteria for mABI and sABI

The term acquired brain injury (ABI) is used to describe the full range of brain injuries occurring after birth. Any injury to the brain which is neither hereditary, congenital, degenerative, nor induced by birth trauma is an ABI. An ABI affects the physical and functional integrity of nerve cells in the brain, resulting in a change of neuronal activity (Brain Injury Association of America, 2019). Depending on the etiology and severity of the event, ABIs can be further classified as non-traumatic or traumatic and mild (mABI), moderate, or severe (sABI) respectively. Non-traumatic ABIs are caused by an internal force such as a stroke, seizure, or toxic exposure. Traumatic ABIs are caused by an external force stemming from assaults, falls, or other accidents. Impact injuries that are traumatic can be categorized as open or closed depending on if the injury is penetrating or non-penetrating (Brain Injury Association of America, 2019). These types of injuries are products of a force which initiate opposing movement between the brain and the skull resulting in collision.

A person may have an ABI if the onset or worsening of the following symptomology appears immediately following the event: a loss of consciousness, loss of memory just before or after the event, an alteration in mental state baseline, or focal neurological deficits such as weakness or impaired speech or vision. The symptoms of an ABI may or may not persist. As a result, individuals who have sustained a mABI may not have the factors listed above medically documented. Lack of the event being classified as an emergency or the realities of certain medical systems compound that challenge (American Congress of Rehabilitation Medicine, 1993). Despite traumatic mABI being the most common traumatic ABI, it is the least understood and the most difficult to diagnose (Mckee & Daneshvar, 2015). Today, traumatic ABI is considered a silent

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epidemic due to its high incidence, significant potential for disability, and impact on the economy (Ianof & Anghinah, 2017).

The severity of an ABI can be considered mild, moderate, or severe based on the Glasgow Coma Scale, the loss of consciousness, and the development of post-traumatic amnesia (Mckee & Daneshvar, 2015). In order for an ABI to be considered mild, an initial Glasgow Coma Scale must be no lower than 13 after thirty minutes. Additionally, post traumatic amnesia cannot exceed twenty-four hours, and any loss of consciousness must not surpass a thirty-minute period. This definition of mABI can be applied to injuries resulting from a direct impact to the head, the head striking an object, or an acceleration/deceleration motion without a direct external head trauma, such as whiplash (American Congress of Rehabilitation Medicine, 1993). It is important to note that this definition does not apply to non-traumatic ABIs. A Glasgow Coma Scale score between 9 and 12 suggests a moderate ABI and a score from 3 to 8 indicates a sABI (Brain Injury Association of America, 2019). Amnesia or a loss of consciousness for longer than mABI diagnostic criteria can also elevate a medical diagnosis from mild to more severe.

ABI Symptoms and Prognosis

As estimated by the Centers for Disease Control and Prevention, traumatic ABIs accounted for some 2.5 million hospital encounters and deaths (CDC, 2015). The symptomology of brain injuries can be physical, cognitive, and behavioral in nature. The effects of mABI primarily include lethargy, vomiting, and dizziness. It is also possible to experience a brief loss of consciousness or memory loss surrounding the event. Upon waking from a loss of consciousness, individuals are often in an altered emotional state of increased anger and irritability. However, some individuals with mABI experience very little symptomology and their injuries may not show up on

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neuroimaging tests (Brain Injury Association of America, 2019). This makes diagnosing mABI difficult. The prognosis for mABI is very positive, with a rapid and full recovery likely. Acute outcomes resolve in approximately two weeks, while a full recovery is expected by ninety days. About 10-15% of individuals remain symptomatic for significantly longer. This outcome is termed post-concussive syndrome, or postictal state, and is difficult to predict due to limited prospective study literature available on the syndrome (Eme, 2017; Fisher & Engel, 2010).

Those with a sABI have more significant effects from their injury including coma (unconsciousness greater than twenty-four hours) with no sleep or wake cycle while unconscious. Injuries are present on neuroimaging tests. Depending on many factors including the severity of the injury, the individual may remain in or emerge from the coma. They can also experience an increased level of consciousness. The effects of a moderate to sABI can be long-lasting or even permanent. A sABI can put an individual into a minimally conscious or persistent vegetative state. It can even cause brain death and ultimately be fatal (Brain Injury Association of America, 2019).

Electrophysiological Correlates of ABI

The EEG provides a productive way to understand neurobiological dysregulation and has evaluative potential in regard to neurotransmission (Sur & Sinha, 2009). However, significant controversy exists over the efficacy and accuracy of EEG as a diagnostic approach to ABI. Psychophysiological correlates, like small time-locked voltages generated by brain structures in response to sensory, motor, or cognitive events, may be predictive of ABI severity (Sur & Sinha, 2009). These signals are known as event-related potentials (ERP) and are single events, which may consist of an increase (e.g. P300) or a decrease (e.g. N300) of potential that occurred at the same time after a given stimulus event. Thus far, reports of high specificity discrimination only exist

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between healthy adults and a carefully selected ABI population in clinical settings. While it is likely such methods will allow for a healthy adult to be discerned from a clinical patient, they are unlikely to provide the resolution necessary to distinguish between major depressive disorder, bipolar disorder, or ABI, for example (Rapp, et al., 2015). The literature is undecided on whether ERPs and oscillatory activity from the EEG may offer insightful data concerning ABI. Intuitive results like those from the Morton and Barker (2010) study show that individuals with more severe ABI have greater impairment. However, some have argued that traditional ABI severity measures, such as the Glasgow Coma Scale, do not accurately predict chronic cognitive impairments post brain injury. In support of this, Karzmark (1992) found that severity of ABI yielded only a modest predictive power on cognitive impairment (Dockree, & Robertson, 2011). While a complete review of all the electrophysiological markers identified to date is outside the scope of this thesis, further study of such correlates may be insightful in implicating EEG as a diagnostic tool and in predicting the severity of ABI.

EEG Brain Injury Detection

The detection of ABI through EEG has been conceptualized previously because traumatic mABIs result in neuronal dysfunction (Ianof & Anghinah, 2017). Given that a change in neuronal activity would also affect the relative dipoles underlying scalp potentials, it makes sense that EEG would be affected as it is known to pick up the related physiologic effects (Rapp, et al., 2015). The first neurodiagnostic assessment to reveal abnormal brain function after traumatic ABI was EEG (Ianof & Anghinah, 2017). After a traumatic mABI, one study found that 86% of patients with an abnormal neurological examination had an abnormal EEG, while only 23% of patients with abnormal EEG had an abnormal neurological examination (Koufen & Dichgans, 1978). Therefore,

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it has been postulated that clinical neurological examination may be less sensitive than EEG measures (Ianof & Anghinah, 2017). However, it is important to note that EEG abnormalities observed in patients with brain injuries are not uniform. This is due to differences in the severity of the injury and the location. Some patients may have a clinically normal EEG fifteen minutes after a concussion (Dow, Ulett, & Raaf, 1944). A recent meta-analysis revealed acute changes after a traumatic mABI including immediate epileptiform activity consisting of high frequency discharges or high amplitude sharp waves followed by one to two minutes of diffuse suppression of cortical activity, further followed by diffuse EEG slowing, which usually returns to baseline within an hour. Software-assisted data analysis allows for quantitative EEG (qEEG) interpretation, which recurrently depicts immediate reduction of average alpha frequency, with augmented theta, delta, or theta:alpha ratio. Despite these trends described in the literature, there are currently no clear EEG or qEEG features unique to traumatic mABI (Ianof & Anghinah, 2017). This literature is not without contradictions either. A recent study comparing the neurophysiological findings of a population with very mild traumatic brain injury (Glasgow coma score 15) and healthy controls utilized EEG and magnetic resonance imaging. However, EEG recordings revealed no focal changes or generalized slowing (Voller, et al., 1999). While conventional EEG is important for posttraumatic epilepsy evaluation, qEEG appears most promising as a diagnostic tool for detecting brain injury (Ianof & Anghinah, 2017; Rapp, et al., 2015). There is also evidence for the ability of EEG to discriminate between mABI and sABI (>90% accuracy) during the post-acute period. While a multivariate vector allows EEG to be the most predictive, frontal and temporal electrode sites were commonly observed to be more statistically significant than other sites (Thatcher, et al., 2001). This finding aligns with the known biomechanics, which make frontal and temporal lobes vulnerable to injury (Ommaya, Thibault & Bandak, 1994).

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This Study

In this study, preexisting Raskin Lab EEG data of healthy, mABI, and sABI groups were gathered utilizing the West and Ross-Munroe (2002) experimental paradigm and were analyzed. Using a Fourier transform to decompose ERPs into their constituent frequencies, power spectra in the frequency domain were calculated for each EEG electrode location for all subjects. A function allowed for an unknown participant to be compared to both the like-group and unlike-group, to determine best correlation between the unknown and the group mean frequency spectrum. A systematic comparison of each rhythm's predictive power in correctly classifying a participant into each of the three groups was conducted to determine the most accurate predictor, with predictive power was defined as having the largest ratio of predictive accuracy to prediction by chance. Results were interpreted with respect to the efficacy of EEG as a diagnostic tool in ABI.

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Questions and Hypothesis

Question 1

Are there electrophysiological differences in the frequency domain of healthy, mABI, and sABI individuals completing a cognitive task?

Question 1 Hypotheses

- Neural systems underlying cognition will be affected by brain injury
- The deficit of an individual will be commensurate with the severity of their brain injury

Question 1 Predictions

- Differences in electrophysiological activity between healthy and ABI adults will reflect the functional deficit caused by their injury
- Healthy adults will have frequency differences in brain regions associated with ABI

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Question 2

Will frequency differences across healthy, mABI, and sABI individuals yield an accurate predictive model for ABI?

Question 2 Hypotheses

- Intergroup frequency changes will be significant enough to classify an unknown participant into their correct group
- The magnitude of difference from healthy baseline will be related to the severity of the brain injury

Question 2 Predictions

- Frequency differences between healthy, mABI, and sABI individuals will allow for a reliable and novel way to diagnose ABI and severity

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Methods

Note on Previously Collected Data

The data used in this study were previously collected at Trinity College, Hartford, Connecticut in the Pedro, 2015 thesis study approved by the Trinity College's Institutional Review Board as described below in the following pages. This study was an investigation of the relationship between clinical and physiological measures of PM, which utilized a two-step procedure. In the primary step participants were evaluated using the Memory for Intentions Screening Test as a clinical measure. The secondary step consisted of an electrophysiological measure consistent with the West and Ross-Munroe (2002) experimental paradigm. The complete procedure took two hours per participant.

Participants

Participants classified as HA and participants with mABI were recruited from the Trinity college staff and student body communities. A population with sABI was recruited from the Brain Injury Alliance of Connecticut, facilitated by Dr. Sarah Raskin, PhD. This study's control group was formed by healthy participants (n = 36). One experimental group was comprised of participants with mABI (n = 15) and the other of participants with sABI (n = 30). Demographic and clinical information for each group was obtained (See Table 1). All participants provided written informed consent prior to the start of their engagement with the study.

The inclusion criteria for healthy adults (HA) consisted of an education greater than 12 years in length, normal or corrected to normal visual and auditory functioning, the absence of a confounding neurological disorder or psychological illness (e.g. Multiple Sclerosis, Parkinson's

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Disease, Epilepsy, Major Depressive Disorder). Participants also were right-handed and learned English as their first language. Recruitment for HA also excluded people with significant difficulty functioning independently, in treatment for substance abuse or dependence, hospitalized for a psychiatric condition, with a diagnosis of HIV/AIDS, who had suffered a loss of oxygen to the brain (anoxia), or who suffered a sABI.

Recruitment for participants with mABI was conducted with the same inclusion criteria as HA with the additional inclusion criterion of having a mABI that occurred at least six months prior to the study.

Recruitment for participants with sABI was conducted with the same inclusion criteria as HA and mABI with the additional inclusion criterion of having a sABI that occurred at least one year prior to the study.

Participants received financial compensation in the form of \$15 gift certificate to a restaurant or the Trinity College Bookstore for their participation in this study.

Table 1: Participant demographic and clinical information by group

Participant Demographic & Clinical Information

	HA	mABI	sABI
Number of participants	36	15	30
Male	11	7	17
Female	25	8	13
Years of Age***	41.54 ± 17.44	20.00 ± 2.37	45.00 ± 16.39
Years of Education**	17.27 ± 3.68	15.17 ± 1.27	14.00 ± 2.98
Etiology of ABI	N/A	concussion (15)	motor vehicle collision (21), fall (5), neurological disorder (1), cerebrovascular accident (2), encephalitis (1)

One-way post hoc ANOVA significance; *p < 0.01, **p < 0.001 (Adapted with permission from Pedro, 2015)

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Clinical Materials and Procedure

The clinical manifestations of PM were assessed using the MIST, a timed 30-minute test aimed at quantifying a person's time and event-based PM. Participants are given a word-search puzzle to complete as a distractor task while performing a series of time and event-based prospective memory tasks. This distractor task simulates the ongoing activity of daily life that occurs while we simultaneously remember future tasks. One example of a time-based task was, "In two minutes, tell me a time of day when I can call you tomorrow" where as an event-based task was, "When I hand you an envelope, self-address it." Subjects are asked to respond to a time or event-based task with either a verbal response or action. Time delays of either 2 minutes or 15 minutes exist between the time when a task is given and the correct time for the corresponding response. After the task-response portion of the test is complete, eight multiple-choice recognition questions are asked of the participant. One example of these questions is, "At any point during this test, were you supposed to... 1. ask me when the session ends? 2. ask me what time the office closes? or 3. ask for your medical records?" If answering correctly, the participant would answer, "yes" and say which one of those three things they were asked to do. According to the MIST Professional Manual, correctly answering these recognition questions reliably shows that an individual has effectively encoded the intention. If recognition is poor, this indicates that the individual did not successfully encode the intention (Raskin, Buckheit and Sherrod, 2010). The last component of the MIST is a final time-based task with a 24-hour delay, which asks participants to call the lab after 24 hours have elapsed from the time of testing. This element is designed to simulate prospective memory time delays in daily life (Raskin et al., 2010). A statistical analysis

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of the MIST variables was done between participant groups using paired-sample t-tests and one-factor ANOVA comparisons ($p < 0.05$).

The physiological correlates of PM were investigated in this study by EEG. A Compumedics Neuroscan Quik-Cap with 64 sewn-in cap electrodes and six external electrodes was used for electrophysiological data collection. External electrodes were placed above, below, and to the side of each eye, which recorded vertical and horizontal eye movement. All electrodes were calibrated to the reference electrode in the center of the cap during the recording. During data analysis electrodes were then re-calibrated to the mastoid electrodes. The stimulus design was modeled after West and Ross-Munroe (2002) and displayed on a computer monitor using E-Prime software. Participants responded to the visual stimulus by pressing one of four marked options on a standard computer keyboard.

Electrophysical Materials and Procedure

The electrophysiological recording step of the experiment took approximately 90 minutes to complete with preparations for recording not exceeding 30 minutes. Once recording, the test was approximately 45 minutes in length and another 15 minutes was allotted for cleanup.

The testing session began with the preparation. Thirty milliliters of Compumedics Neuromedical Supply Supplies Quik Gel conductive gel were placed in a ceramic microwave safe container and heated for 20 seconds. Two blunt BD 16G 3/4 blunt square grind precision glide needles, attached to BD 10ml Luer-Lok tip, (latex free) syringes were filled with 10ml of conductive gel. The participant was then asked to wipe their face using a facial wipe, especially at the sites of electrode placement: their temples, above and below their eyes, and their forehead where the front of the cap will rest. To achieve reduced impedance, subjects were asked to abrade

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their head using a wide tooth hairbrush. The head of the subject was then measured from the nasion to the back of the head to establish the correct cap position. Then, the circumference of their head was measured and 10% of the circumference was calculated. That distance was measured from the back of the head towards the front and the cap was subsequently placed to fit these measurements. This allowed the cap to fit snugly with the front of the cap on the forehead of the subject above the bridge of their nose.

After the cap was properly fitted, the six external electrodes were placed around the eyes and on the mastoid bones behind the ears. The electrodes placed around the eyes were positioned on the side of the left eye (HEOL) and the right eye (HEOR) as well as below (VEOL) and above the left eye (VEOU). The mastoid electrodes (M1 and M2) were placed on the left and right mastoid bones respectively. Each external electrode was secured in place using Compumedics v-shaped electrode washers. These held the electrodes firmly in place and allowed for conductive gel to be inserted.

The cap was then plugged into the Neuroscan head box, which was attached to the SynAmpRT amplifier. Both pieces of hardware were connected to Scan 4.5 software that monitored the electrode impedance. Next, a small amount of gel was inserted into each electrode to increase scalp conductance. Over-gelling was avoided so that no gel leaked from underneath the electrodes. Excess gel can cause electrodes to become interconnected across the cap. This phenomenon, known as salt-bridging, was carefully monitored for because it is known to compromise EEG readings. Without gel, the impedance for each electrode was approximately 50.0kOhms. This was displayed as a magenta color within the Scan 4.5 electrode montage. With the gel, impedance readings dropped to as little as 5kOhms. The color of the electrode montage became dark navy blue or black to represent this change.

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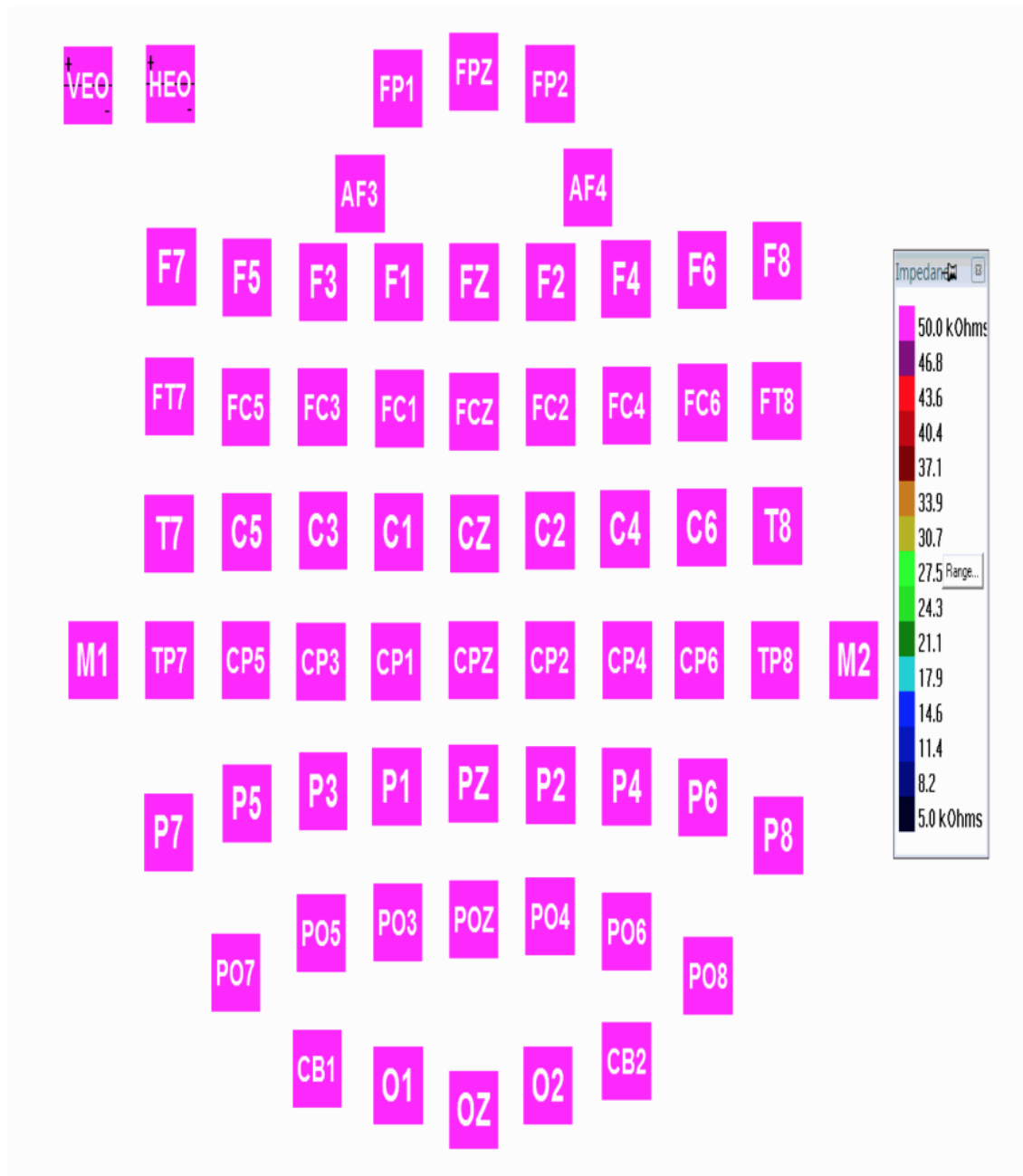


Figure 1: Neuroscan 64 electrode EEG cap montage before conductive gel application. (Reproduced with permission from Pedro, 2015)

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Experimental Paradigm Design

The experimental paradigm was modeled after the West and Ross-Munroe (2002) study. This design measures prospective memory using event-based tasks. Similar to the MIST, this paradigm contains a short time delay (~10-20 seconds) between the appearance of a PM cue and the chance to realize the intention. However, the MIST provides an opportunity to examine PM performance with longer time delays (2 minutes, 15 minutes, and 24 hours). Thus, the combination of the behavioral and physiological PM measurement used in this study was able to provide a robust assessment of the relative PM of an individual.

Every participant completed 10 sessions, each containing 102 word pairs or letter strings total for the ongoing activity, intention formation, and PM cue trials. To ensure participants understood the tasks, a training session containing each type of trial was completed prior to the test sessions.

On ongoing activity and PM trials, a semantically related or an unrelated word pair was presented in lower-case letters. Each pair appeared on a computer monitor horizontally and vertically centered, stacked one on top of the other until a response was made. The first pair appeared after the spacebar key was pressed to start the activity. The selection of word pairs was created through the collaboration of Navneet Kaur '12 and Dr. Robert West. However, after a test trial, several words were removed due to their potential to trigger unpleasant emotional responses based on their semantic meanings. Any words perceived to be explicitly linked to trauma and/or violence were subsequently omitted. During the ongoing activity trials, word pairs were presented in red, green, blue, and purple. Both words were presented in the same color for half the trials and different colors for half the trials. At the beginning of each session, participants were directed with standardized instructions to press the key labeled 'same' (the 'N' key covered with a label 'same')

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with their right index finger if the word pair is semantically related and to press the key labeled 'different' ('M' key covered with a label 'different') with their right middle finger, if the word pair was not semantically related. For example, if the word pair 'opal' (in blue) and 'topaz' (in purple) was presented, then the participant should press the 'same' key because the words are semantically related. Conversely, if the word pair 'physics' (in red), and 'rose' (in red) was presented, then the participant should press the 'different' key because the words are not semantically related.

On intention formation trials, the word pair was replaced by two letter strings presented in either light gray or magenta (i.e. c-c-c-c-c in light gray, c-c-c-c-c in magenta, v-v-v-v-v in light gray, or v-v-v-v-v in magenta). During intention formation trials, participants were asked to form the intention to press the key associated with the letter the next time a word pair was presented in that color (West & Ross-Munroe, 2002). Thus, if 'c-c-c-c-c' was presented in magenta, then the subject should press the 'C' key when the next magenta word pair is presented. After forming the intention, participants should press either the 'C' or 'V' key, depending on which letter string was presented on the screen, to proceed to the next trial. It should be noted that this part of the experimental design was adapted from Kaur (2012) and differs slightly from the West and Ross-Munroe (2002) procedure where the 'N' or 'M' key needed to be pressed to move past the intention formation stage.

On PM cue trials, word pairs were presented in the color that corresponded to the letter string presented in the preceding intention formation trial (i.e. either light gray or magenta). During these trials, instead of making a semantic judgment, participants were able to press the key (i.e. 'C' or 'V') associated with the color displayed in the last intention formation trial. After each

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response, the screen was blank for 500ms before the word pair or letter string for the next trial was presented.¹

The Current Study

In the current study, we analyzed previously collected data as described above. This data contained average evoked potential data of each participant at 66 electrode locations over 1.4 seconds (n=80). Participants fell into one of three conditions: healthy (n=35), mABI (n=16), or sABI (n=29). Data were uploaded into MATLAB for analysis. A Fourier transform was utilized to decompose the time-locked potentials into their constituent frequencies. In essence, data was examined for distinctive properties in the frequency domain that were predictive of ABI, which were not immediately apparent in the traditional data analytic approach relying on ERPs. Using the related frequencies from 1-100Hz, a function was created by which to compare a participant with their like-condition. In this way, participants could be categorized as more like one condition compared with the other two. By adjusting the frequencies, our function could be calibrated to focus the data into specific EEG rhythms (i.e. delta, theta, alpha, beta, and gamma). A systematic comparison of the predictive power of each rhythm in correctly classifying a participant into each of the three groups was conducted to determine the most accurate predictor. Predictive power was defined as having the largest ratio of correct classification to correct classification by chance. A list of all indicator electrode locations was generated for the most predictive rhythm in the classification of each group. These electrode locations were mapped onto the brain based on EEG positioning of the electrodes during recording for a better understanding of the brain regions involved in ABI.

¹ All methodology described above was adapted with permission from Pedro, 2015.

Results

Regions of Interest

A number of electrode locations were identified as predictive while sampling individual or all brain rhythms for each ABI group (See Figure 3). In the case of healthy participants, electrode locations 48 and 50 most accurately predicted their correct placement into the healthy adult group when all brain rhythms were being sampled. However, participants that had suffered either an mABI or sABI were most accurately classified into their respective group by a number of electrode locations while sampling was restricted to the theta rhythm (4-7Hz) (See Tables 2 & 3).

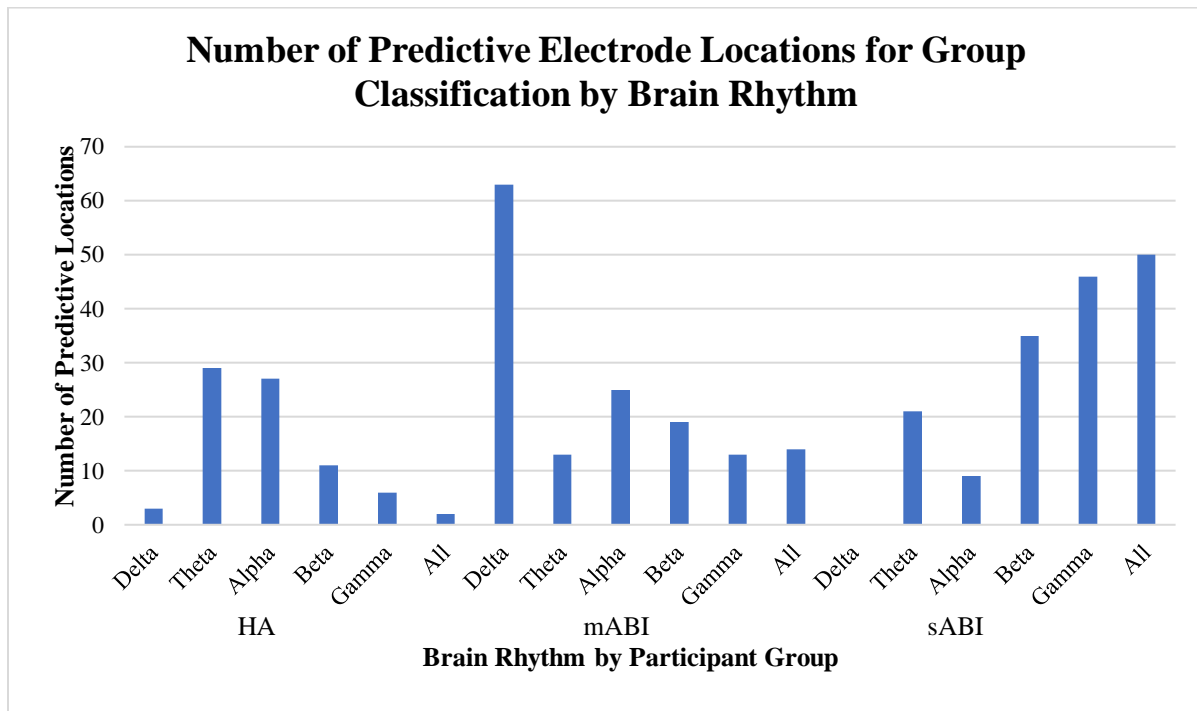


Figure 3: The number of electrode locations determined to be predictive in determining participant group by brain rhythm

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Table 2: The relative accuracy of group classification with respect to participant group and rhythm
Accuracy of Participant Classification

	Delta	Theta	Alpha	Beta	Gamma	All
HA	0.5500	0.5207	0.5241	0.5500	0.5458	0.6125
mABI	0.4308	0.5423	0.4930	0.5007	0.5269	0.5143
sABI	Undefined	0.5411	0.4861	0.5321	0.5242	0.5158

Table 3: The indicator electrode locations for the most predicative rhythm of each participant group

Electrode Indicators of ABI

ABI Groups	Predictive Electrode Locations at Most Accurate Rhythm
HA (All)	48, 50
mABI (Theta)	9, 12, 17, 18, 19, 20, 25, 28, 40, 44, 45, 53, 61
sABI (Theta)	4, 5, 7, 8, 10, 13, 14, 15, 22, 24, 32, 35, 48, 50, 51, 52, 56, 60, 62, 63, 66

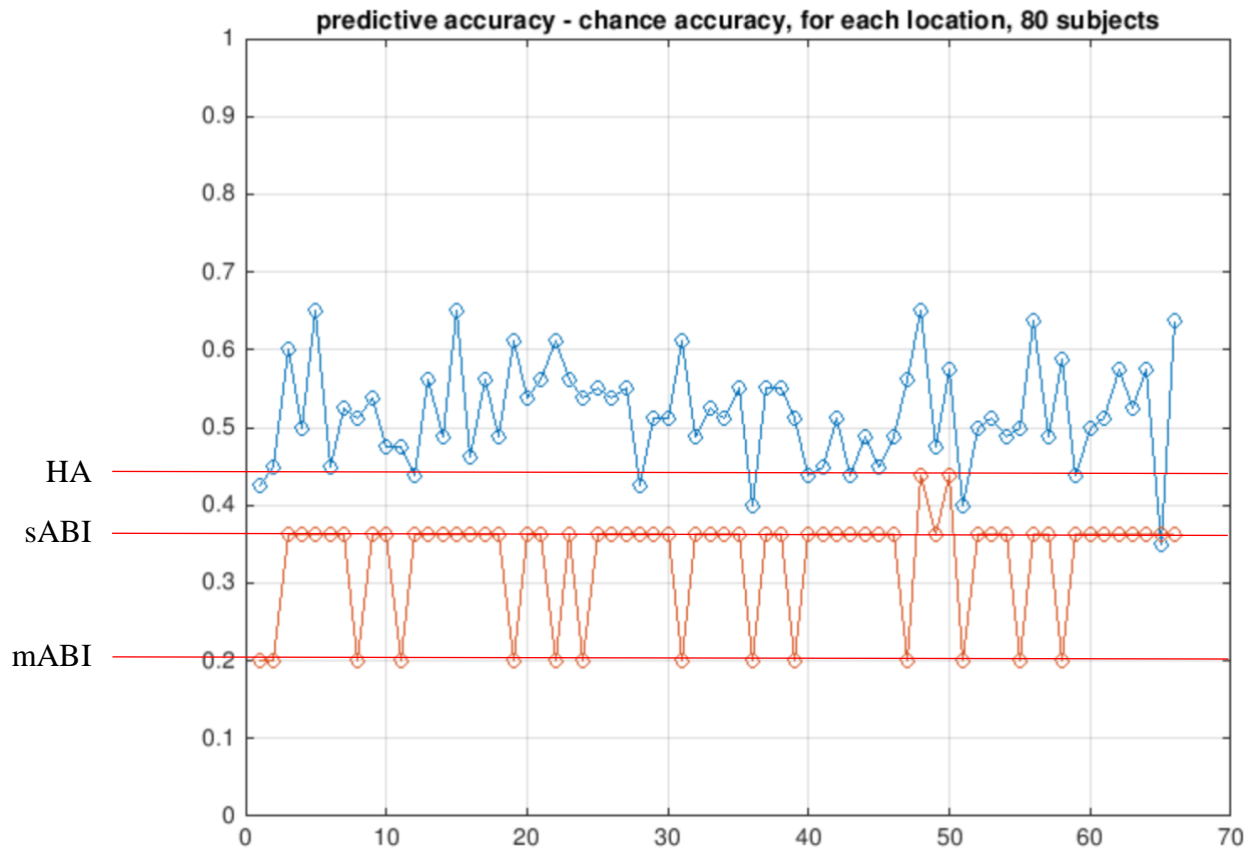


Figure 4: The accuracy of a participant being correctly classified into their respective group sampling all brain rhythms (blue) and by chance (orange) for each group at every electrode location

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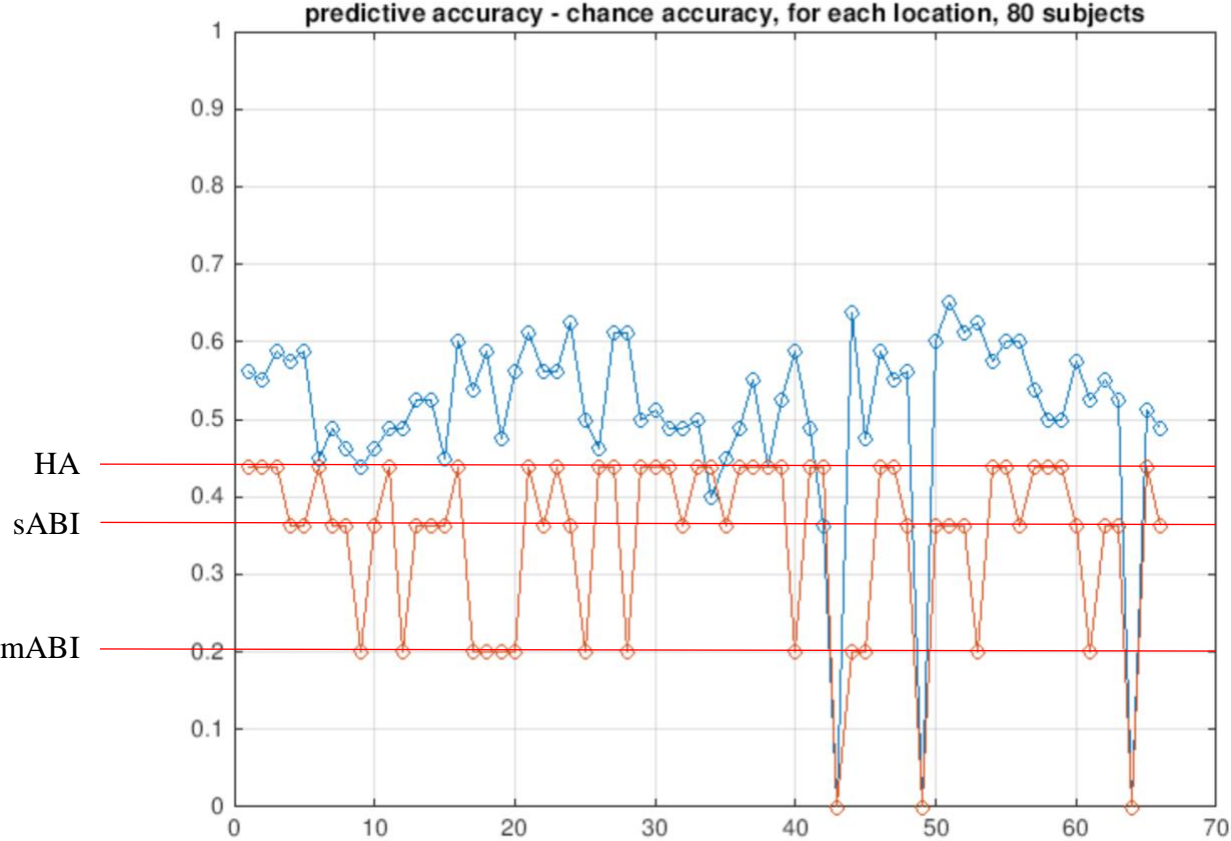


Figure 5: The accuracy of a participant being correctly classified into their respective group sampling theta rhythm (blue) and by chance (orange) for each group at every electrode location

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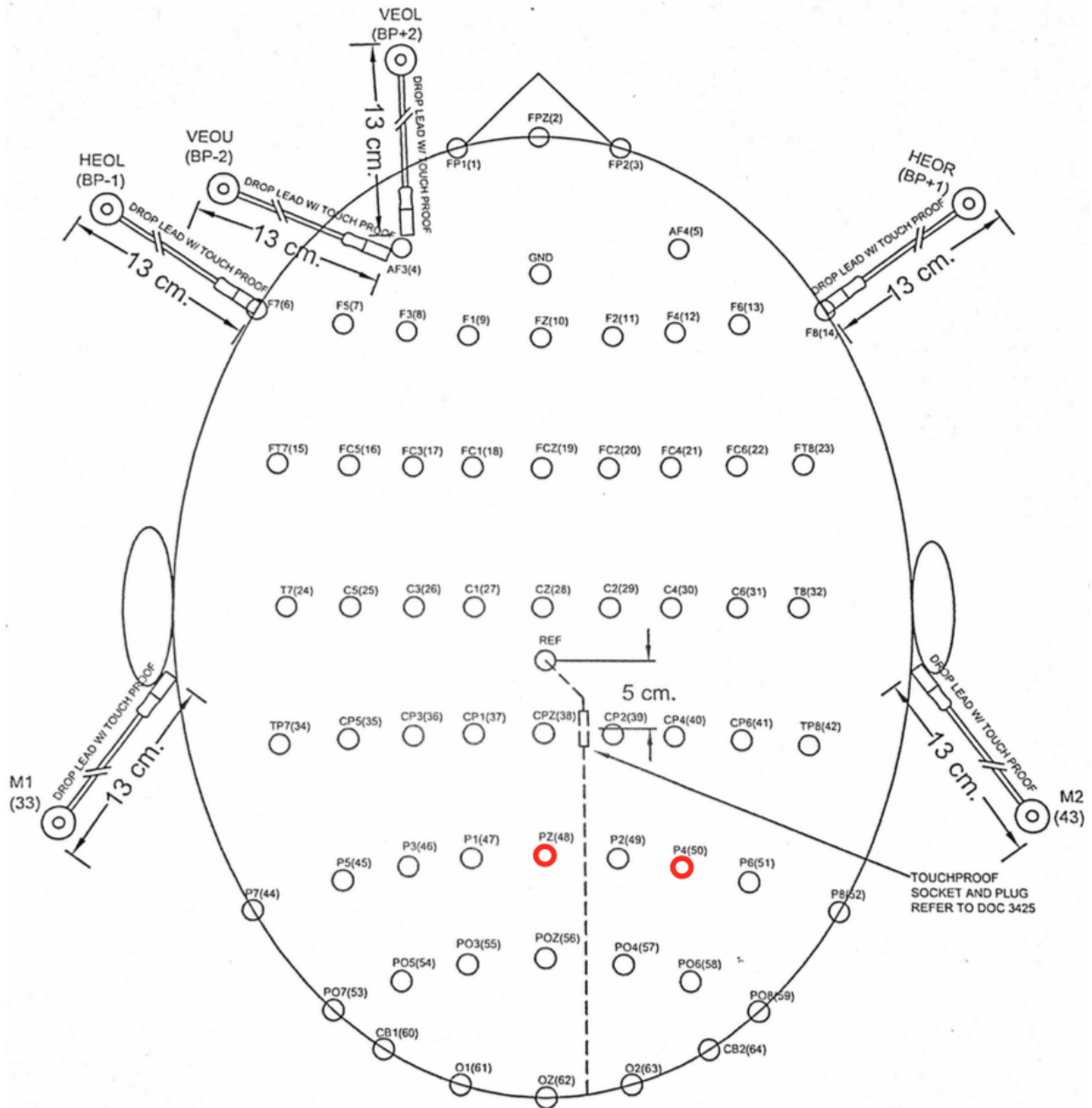


Figure 6: Compumedics Neuroscan 64-channel Quik-Cap with Healthy Group electrode locations shown in red (all rhythms sampled)

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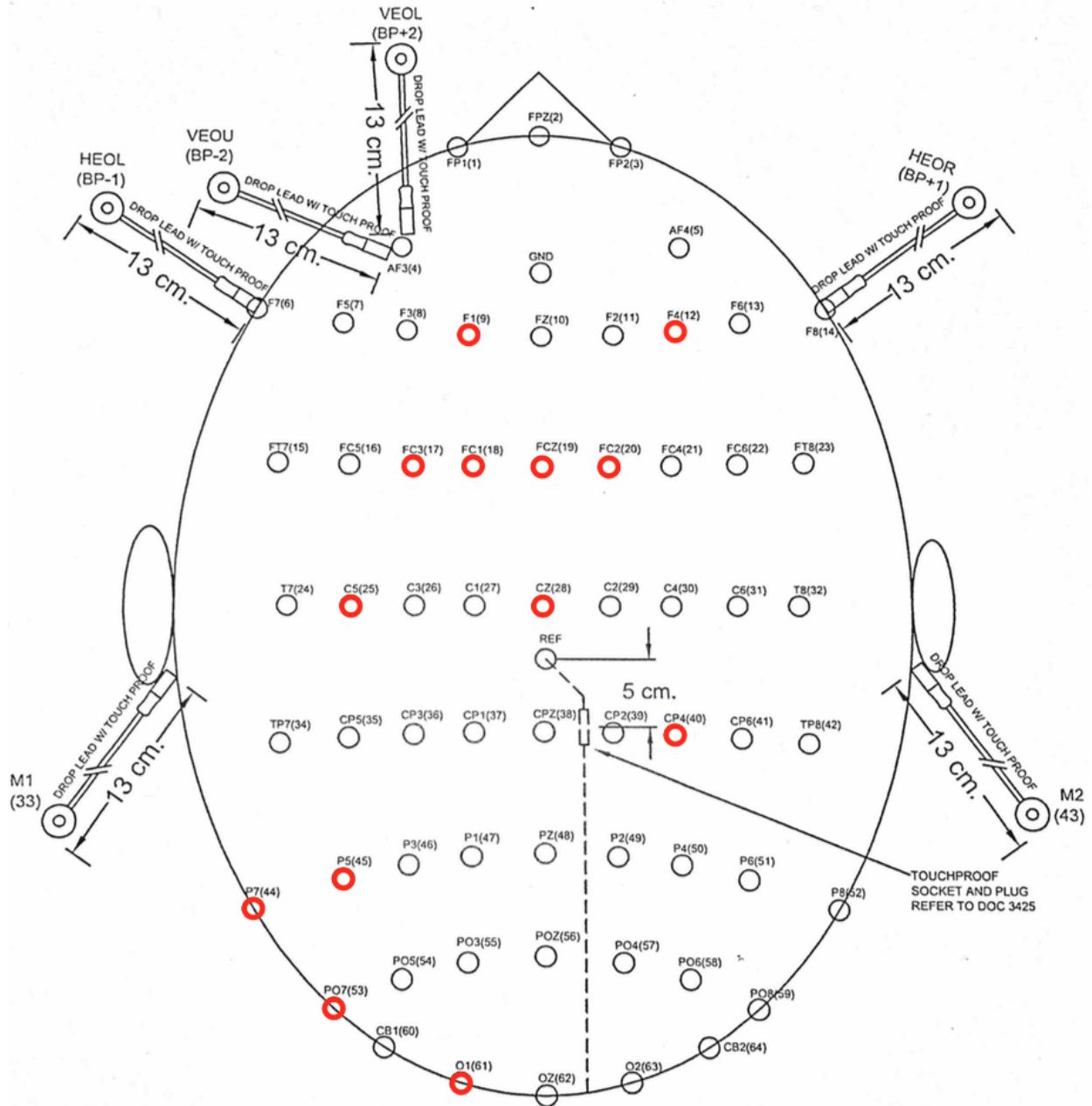


Figure 7: Compumedics Neuroscan 64-channel Quik-Cap with mABI Group electrode locations shown in red (theta rhythm sampled)

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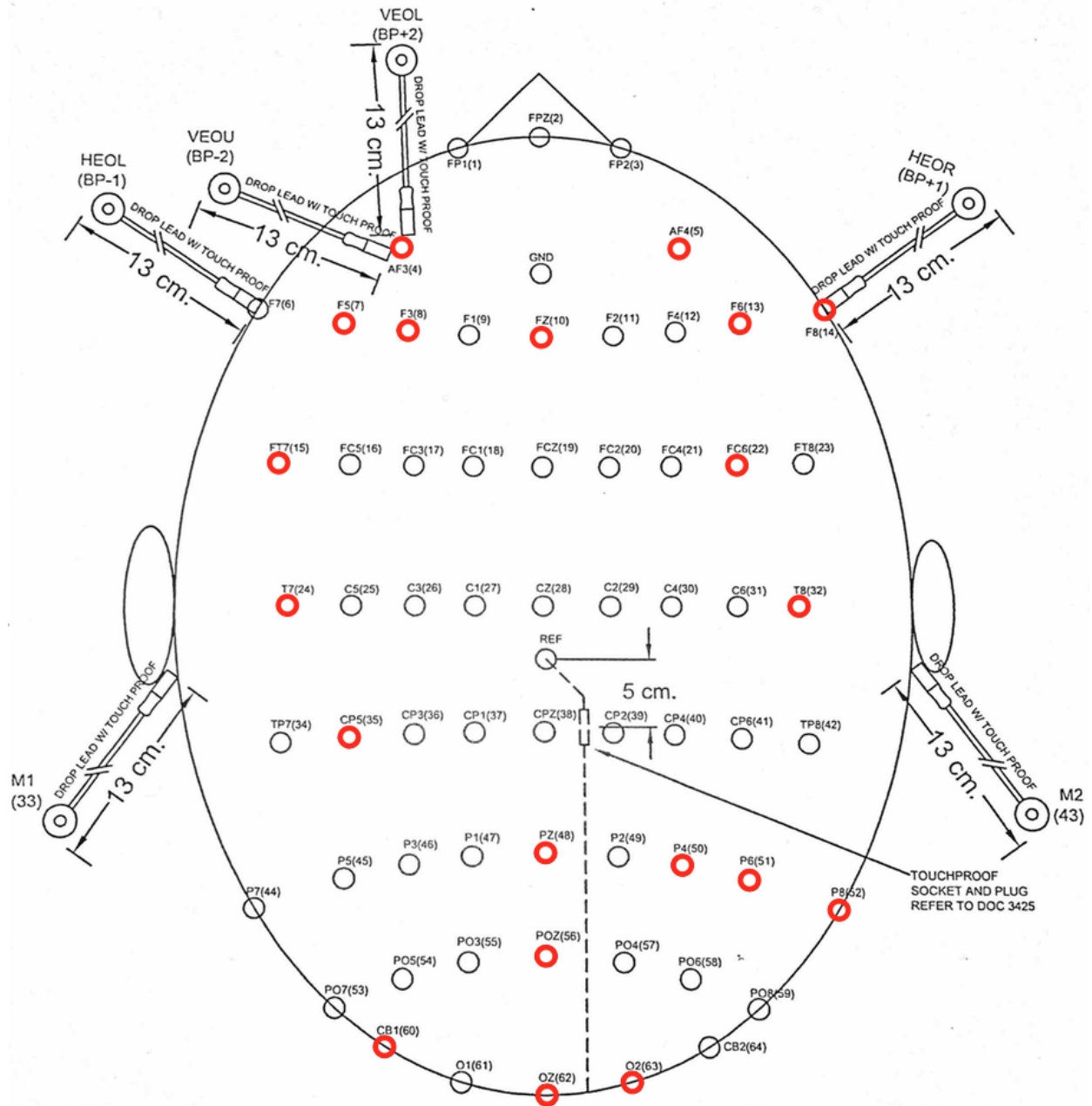


Figure 8: Compumedics Neuroscan 64-channel Quik-Cap with sABI Group electrode locations shown in red (theta rhythm sampled)

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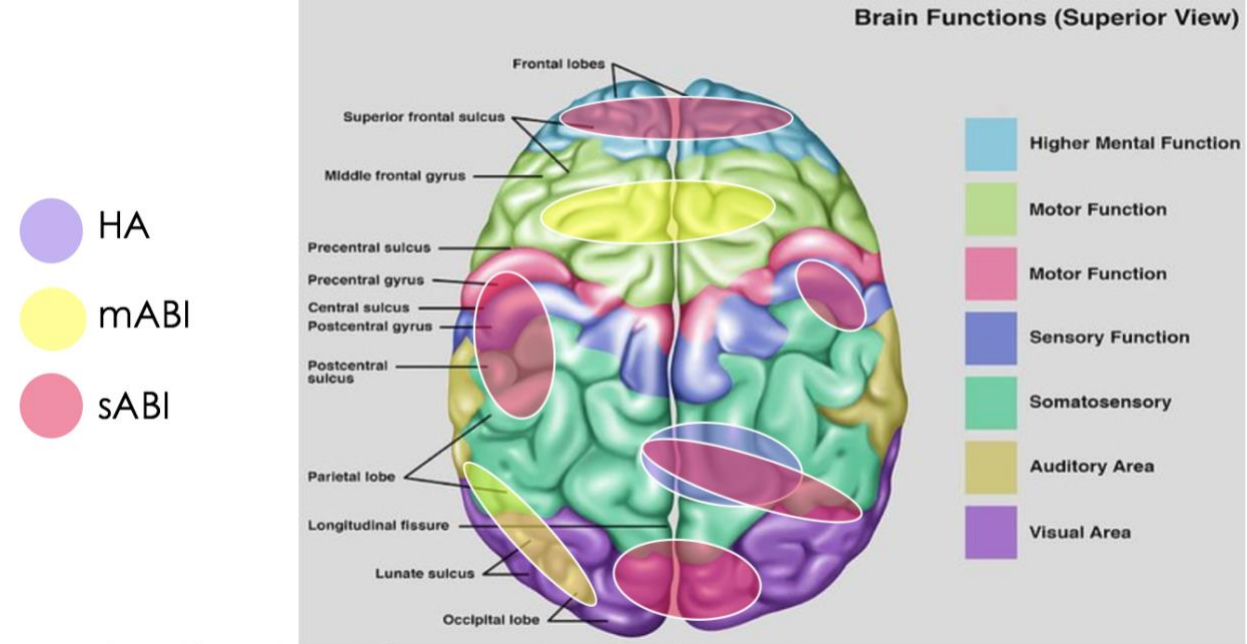


Figure 9: A superior view diagram of the human brain with HA, mABI, and sABI predictive regions mapped accordingly

Discussion

Rationale

Mild brain injuries are the most common but are the least well understood and the most difficult to diagnose (Ianof, & Anghinah, 2017; Mckee & Daneshvar, 2015). Because of this, mABI may go undiagnosed and untreated, resulting in delayed recovery or social deficit. The latter is exasperated by misdiagnosis, which can lead to unnecessary intervention for contrived behavioral, cognitive, and somatic problems (Zasler, 1993). Due to high incidence, potential for disability, and resulting economic impact, brain injury— especially mABI—is considered a silent epidemic (Ianof & Anghinah, 2017). Thus, a reliable way of quickly diagnosing such injury is necessary to alleviate negative outcomes. Electrophysiological differences have been found to exist between degrees of ABI, allowing for the EEG to be conceptualized as a diagnostic tool. However, previous studies have exclusively examined time-locked EEG ERPs. In the current study we utilized a Fourier transform to study the novel question of whether there are properties in the frequency domain that are distinctive between HA, mABI, and sABI groups that are not immediately apparent in the traditional data analytic approach. We further examined whether such differences would be predictive of ABI severity.

Interpretation of the Results

In examining the frequency domain of HA, mABI, and sABI groups, it was found that differences did exist. Given that each participant completed the same prospective memory task following a standardized protocol, it can be inferred that the observed differences were a result of ABI affecting the underlying neural systems involved in cognition. These differences led to a

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predictive model (as discussed below) not accounted for by typical variability from participant to participant. As found through Pedro's (2015) analysis of this population's performance, the amount of disturbance in a participant's ability to accurately complete the experimental tasks was commensurate with the severity of their brain injury. We found no evidence to refute this interpretation; however, our analysis does not allow us to confirm an additive effect when injury is more severe. Rather, the sABI group seems to have somewhat different brain regions that are predictive of injury compared with mABI. This does not represent a difference in the level of disturbance within the neural systems of participants, but a difference in the systems affected. It was because different neural systems were implicated in mABI and sABI that a predictive model was able to be created based on varying electrode locations implicated (See Table 3). Intergroup variance was significant enough to classify a participant with an unknown ABI status into their correct group with an accuracy of greater than 50% when sampling the theta rhythm in isolation (See Table 2). There was also evidence supporting the notion that the magnitude of difference from healthy baseline will be related to the severity of the brain injury. This can be seen in the overall increase in number of predictive locations for each group's most predictive rhythm (See Figure 3 & Table 3). Each predictive location was then mapped onto an EEG map by condition (See Figures 6, 7, & 8) and collectively onto a brain image (See Figure 9). It can be seen that as ABI becomes more severe that, in addition to having more predictive region overall, the regions become more diffusely located. The locations of HA correlates are acutely located at medial areas in the parietal lobe, whereas correlates of ABI are somewhat shifted to frontal and occipital lobe regions. This is significant because these regions are where ABIs are most likely to be sustained (Rapp, et al., 2015; Duff, 2004). The lateral predictive locations of sABIs offer further support for this interpretation. It would likely take severe trauma to be able see effects in these locations from

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either frontal or occipital insult. Lastly, it is important to draw attention to the overlapping region indicative of HA and sABI. This region may indicate that a lack of injury is predictive of health or, more likely, that an injury at this location indicates severe trauma. However, either perspective justifies raising the question of why HA and sABI predictive sites overlap. This may be an unanticipated effect of using different brain rhythms in the predictive modeling of HA and people with ABI. Additionally, it may mean that sABI locations that are not also predictive of HA are regions that, while unlikely to be injured, are perhaps more likely to have similar activity and function despite mild injury. This overlap could further be an artifact of human error in a misclassification of an sABI individual as HA, which would have caused the medial parietal lobe to appear more significant in ABI prediction overall (See Limitations).

Conclusions

From the current study we found that neural systems underlying cognition are affected by brain injury in a way that is related to the severity of the injury. Furthermore, we found that intergroup frequency changes were significant enough to classify an unknown participant into their correct group and that the magnitude of difference from healthy baseline is also related to the severity of the brain injury. While further study is needed to determine the efficacy of utilizing EGG as a diagnostic tool in ABI, these results indicate promise in analyzing properties of the frequency domain, which are not apparent in traditional data analytic approach, but may be distinctive, thus predictive, in regard to ABI.

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Further Study

In order to confirm the findings above, it is important that further research be established in examining the relations between EEG frequency data and ABI. One future direction of this research could explore whether or not sonification would elucidate further predictive value from the frequency data of evoked potentials. As early as 1934, Adrian and Matthews attempted to convert EEG signal into sound. The notion of making EEG signal audible came early in the history of electroencephalography (Deuel, et al., 2017). This concept of transforming data into sound developed concurrently with neuroimaging techniques because the complexity and fast temporal dynamics of brain activity necessitated more intuitive ways to interpret intricate data. Sound offers a creative way to represent brain activity, which makes real-time EEG sonification useful in many applications (Valjamae, et al., 2013). Furthermore, techniques of sonification often elucidate sophisticated patterns of activity difficult to notice through traditional data analytics. Efforts toward real-time EEG sonification have yielded diagnostic alternatives to purely visual feedback along with possibilities of therapeutic biofeedback, and even artistic expression (Baier, Hermann, &Stephani, 2007; Deuel, et al., 2017). It is possible to create a brain-computer interface capable of audifying brain activity in real-time through digital instruments (Baier, Hermann, &Stephani, 2007; Deuel, et al., 2017). This type of technology could enable non-professionals to make quick, accurate, and audible diagnoses in a variety of settings. This may be applied during sport competitions where medical personal may not be available or able to make a diagnosis of concussion or another ABI. Moreover, an interface like this may actually have therapeutic benefits through biofeedback (Bergstrom, et al., 2014). Perhaps, certain populations may find benefit in the act of using such a device in a collaborative symphonic setting with others. Those disabled through

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progressive neurodegenerative disease may experience a rise in affect or an improvement in their quality of life due to such an experience (Deuel, et al., 2017).

Limitations

While this study may indicate the promise of EEG as a diagnostic tool, it is important to recognize sample size as a major limitation of this study. While the function we created to classify unknown participants was accurate for our dataset, we are unsure of its generalizability. Due to the small number of participants in any one group, we decided not to set aside participants to test our network. For this reason, it is possible that the accuracy observed in predicting a participant's group within this dataset may be specialized to this dataset. However, the diverse range of our participants' ABI etiologies does give us some confidence that our results are generalizable to other datasets (See Table 1). Furthermore, there was one appreciated instance of human error, which may have affected the results of this investigation. Previously collected data were taken from pre-assembled files listing the participant groups as such: HA (n = 35), mABI (n = 16), and sABI (n = 29). This differs from the demographic information gathered from Pedro, 2015 (See Table 1). One participant was omitted from our study entirely and one sABI individual was incorrectly identified as either HA or mABI. It was not possible to know which participants were left out or misclassified as data was deidentified. This discrepancy was not realized until post-analysis comparisons were made. It is also important to consider that there are changes in brain activity during the weeks post ABI (Rapp, et al., 2015). Time between ABI and EEG recording was not a variable considered when recruiting participants and, therefore, may have confounded our results. Lastly, it is worth noting here that EEG has limitations including those relating to

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source localization and the inverse problem of working back EEG data to estimate sources that fit the relative measurements (Grech, et al., 2008).

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