Exploration and Identification of Neural Correlates in Healthy Young Adults During a Graded Cognitive, Physical, and Combined Task: An EEG Study

by

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Abstract

Returning to play following a sports related concussion remains a controversial process due to the emphasis placed on subjective symptom reporting. The development of an objective measure capable of assessing cortical recovery remains elusive, however EEG has shown promise with its ability to record during exercise. The objective of this pilot study was to examine the association between EEG metrics and behavioural changes in healthy young adults.

The study involved 13 participants who performed a novel graded working memory task, a graded exercise session and a task combining the two together while EEG was recorded over 3 separate sessions. The tasks consisted of 5 levels of increasing difficulty and each participant performed the tasks in a randomized order. Participant heart rate, perceived exertion and accuracy were recorded between levels and tasks. EEG analysis applied power spectrum analysis and graph theoretical analysis to identify cortical activity and cortical networks changes.

When graded exercise and cognition were combined, there was a significant change in behaviour and neural activity compared to when each task was completed individually. The combined task led to significant changes in brain and behavior as seen in EEG activation pattern, power output and frontal functional connectivity measures.

These results suggest that following sports-related concussion individuals would require increased neural resources to complete a combined cognitive and exercise task. Following injury, these additional resources may not be available and result in a decrease in task performance. This data has the potential to be used in addition to existing concussion recovery tests in assuring full recovery prior to the return to play.

Preface

The present thesis contains results from a study completed by the candidate Shaun Porter, under the supervision of Dr. Naznin Virji-Babul. Experimental design and conception was a joint effort between Dr. Virji-Babul and Shaun Porter. The Anti-Saccade and Serial Addition Task, developed by Dr. Noah Silverberg and colleagues, was used in this study with full permission. The candidate was responsible for all data acquisition and analysis, data interpretation, and documentation.

The study and all associated methods were approved by the University of British Columbia (UBC)'s Clinical Research Ethics Board (H15-0214). The author would like to thank Saurabh Garg MSBME and Arnold Young B.Eng. for their tremendous help throughout the data analysis process.

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List Of Abbreviations

ACC: Anterior Cingulate Cortex

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

ASAT: Anti-Saccade Serial Addition Task

ATP: Adenosine Triphosphate

BDNF: Brain Derived Neurotrophic Factor

BESA: Brain Electrical Signal Analysis

BOLD: Brain Oxygen Level Dependent

CBH: Centre for Brain Health

CSF: Cerebral Spinal Fluid

CT: Computerized Tomography

Cz: Central Electrode

DLPFC: Dorsal Lateral Prefrontal Cortex

DTI: Diffuse Tensor Imaging

EEG: Electroencephalography

EF: Executive Function

ERP: Evoked Response

FEF: Frontal Eye Fields

FFT: Fast Fourier Transform

FM: Frontal Midline

fMRI: Functional Magnetic Resonance Imaging

HR: Heart Rate

HRR: Heart Rate Reserve

Hz: Hertz

ICA: Independent Component Analysis

IFG-1: Insulin Growth Factor – 1

LFP: Local Field Potential

LMM: Linear Mixed Model

MEG: Magnetoencephalography

MFG: Medial Frontal Gyrus

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

mTBI: mild Traumatic Brain Injury

PASAT: Paced Auditory Serial Addition Task

PCFDR: PC False Discovery Rate

PCS: Post Concussion Syndrome

PET: Positron Emission Tomography

PVSAT: Paced Visual Serial Addition Task

RPAQ: Recent Physical Activity Questionnaire

RPM: Rotation per Minute

RTP: Return to Play

SEF: Supplementary Eye Fields

SRC: Sports-Related Concussion

TBI: Traumatic Brain Injury

VLPFC: Ventro-lateral Prefrontal Cortex

W: Watts

WCST: Wisconsin Card Sorting Task

WM: Working Memory

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Chapter 1: Overview of Sport-Related Concussion and Recovery

1.1 Sports-Related Concussions

Sports-related concussions (SRC) are prevalent in all age groups and sports. Classified as a mild form of traumatic brain injury (TBI), sport related concussions (SRC) are caused by linear and/or rotational forces exerted on the brain and are defined as temporarily disturbed brain function resulting from a traumatic force [1]. TBI is a serious condition that ranges in severity, from mild to severe and is classified based on the length of time spent unconscious, post-injury amnesia, and the Glasgow Coma Scale in addition to the information derived from neuroimaging [2]. Concussion and mild TBI are both viewed as being on the mild side of the TBI spectrum, and are often presented as one and the same. However, there are significant differences in the classification of these injuries. Mild TBI is classified based on a loss of consciousness for no more than 30 minutes or amnesia, and a Glasgow Coma Score of 13 to 15 (Ref: American Congress of Rehabilitation Medicine and the Centers for Disease Control). A concussion meanwhile, is classified as an alteration of mental status that does not necessarily involve loss of consciousness (American Academy of Neurology). Clinical diagnosis of SRC is based on a combination of subjective symptom reporting, balance testing, neuropsychological testing and clinical exam. Concussion often presents with a diverse number of signs and symptoms, the most common of which being headache and dizziness [3]. Other concussion symptoms include nausea, vomiting, balance problems, fatigue, sensitivity to light or noise, dazed, trouble concentrating, trouble paying attention, forgetfulness, confusion, irritability, increased emotions, drowsiness, increased sleep, difficulty falling asleep and difficulty staying asleep [4]. These symptoms are often grouped into physical, cognitive/emotional and sleep categories and the number and severity of the symptoms vary greatly by individual [5]. The signs and symptoms of concussion can be subtle and present immediately following the injury or in the hours and days to follow. In most cases, symptoms resolve within the first 7-10 days, however in some cases symptoms can persist for weeks to months [6, 7].

Currently a large component of SRC diagnosis and recovery management is based on subjective symptom reporting. In order to improve diagnosis and care following concussion there is a need to develop reliable objective measures for clinical application. Prichep and colleagues (2013) developed an EEG-based discriminant index, to act as an objective measure for concussion recovery and identification, which has shown to be sensitive to the presence of concussion as well as severity [7]. The index was capable of distinguishing concussed individuals even after clinical symptoms and neuropsychological testing scores had recovered. This supports the finding from other studies, which suggests that clinical symptoms and cognitive function are not directly related to brain function[8, 9]. Further research is needed to identify which neurophysiological measures are most sensitive in assessing cognitive function and the impact concussion has on these processes.

1.2 Behavioural And Cognitive Impact Of Concussions

Concussion identification and management relies on a combination of subjective symptom reporting and neurocognitive testing, as neuroimaging has shown difficulties in identifying changes following concussion. Multiple tests have been developed to assess a wide range of cognitive functions and have been suggested to aid in tracking the recovery of the athlete prior to return to play. Concussion has been found to influence a wide range of cognitive functions that include attention and concentration, processing speed, learning, working memory, executive function and verbal fluency [10]. As each concussion is unique, the cognitive domain impacted by the injury can vary greatly both between individuals and between concussions within the same individual. When used to track concussion recovery, neurocognitive testing has shown varying results. A study by McCrea and colleagues (2003) identified impaired cognitive processing and verbal memory in concussed athletes two days following concussion, which along with their reported symptoms had returned to normal by day 7 in the majority of the participants [6]. Fazio and colleagues (2007) found that individuals who were asymptomatic continued to have impaired cognitive function compared to healthy controls [11]. The conflicting results between symptom reporting and neurocognitive testing show the need for more research and the potential role for neuroimaging in the assessment of concussion recovery. A recent systematic review of neurocognitive testing following concussion found a large number of neurocognitive tests, however there were a limited number of studies. The authors stated concerns regarding the adoption of neurocognitive tests into clinical practice while validity and reliability of the tests remain questionable. The authors stressed the importance of being familiar with factors that can influence performance of the tests and considering them in their interpretation [12]. The authors also noted the worrisome trend for athletes to "sandbag" their baseline tests in order to decrease their chance of missing playing time if they suffer a SRC. The incorporation of neuroimaging alongside the neurocognitive testing provides an increased level of objectivity in assessing SRC recovery.

1.3 Neurometabolic Impact Of SRC

Initial concussion models used to comprehend the neurophysiological basis of the injury originated from experimental animal studies. These studies showed that following a concussive injury there is an indiscriminate release of excitatory neurotransmitter glutamate, in addition to a large depolarization of neurons through a sodium and potassium ionic shift [13]. In order to return the system to homeostasis, a large amount of ATP (adenosince triphosphate) is required and results in an increase in cerebral glucose metabolism [14]. The period of hyperglycolysis can persist for days following injury, with the duration found to be linked to the severity of the injury [15]. These changes require increased cerebral blood flow and if this need is unmet, can result long-term damage to brain cells [16]. Following the hyperacute phase of increased glucose metabolism, there is a prolonged period of metabolic depression that can last 7 – 10 days in adult rats, which prevents the brain from functioning normally and places the brain in a vulnerable state for a secondary injury [17]. In terms of cortical activity, animal studies have shown an immediate suppression of cortical activity following injury. This widespread suppression persisted between seconds and minutes, and was followed by a period of slowed activity that gradually returned to baseline levels within the hour [18].

The neurophysiological response to concussion has been similarly reported in humans, showing the increased release of glutamate and potassium, as well as the changes in glucose metabolism [19]. Using positron emission tomography (PET), changes in glucose metabolism have been recorded in vivo in patients following both TBI and concussion [20]. The neurophysiological changes in the brain post-SRC follow a similar timeframe as the symptom reporting and some neurocognitive studies, suggesting a potential link between the cellular alterations and observable symptom and cognitive results. However, how these neurophysiological changes influence the structural and functional state of the brain remains underexplore and could provide more information regarding any acute damage to the brain and the recovery process following SRC.

1.4 Brain Structure And Function Changes Following SRC

Structurally, studies incorporating DTI have shown anterior regions of the brain to be more vulnerable to injury [21], while functionally, fMRI studies consistently find decreased activation in frontal regions such as right medial frontal gyrus (MFG), anterior cingulate cortex (ACC) and right precentral gyrus [22]. A bilateral decrease in dorsal lateral prefrontal cortex (DLPFC) activation has also been recorded in multiple studies [23-25]. These structural and functional changes occur in regions associated with executive function and working memory performance, and correspond with significant decreases in executive function and working memory task performance.

Another neuroimaging technique, Electroencephalography (EEG) has shown early promise in identifying changes following TBI and concussion. An overall decrease in EEG power has been shown across all frequency bands following concussion [26]. This could be a potential physiological underpinning for the impaired cognitive function seen following concussion. Other changes associated with concussion include increase in hemispherical power asymmetry, decreases in hemisphere coherence [27], reduction of low frequency power and increase in higher beta power around medial frontal brain areas [28], and changes in local connectivity networks in the prefrontal cortex [29]. These changes suggest that following concussion the connections in the brain are altered, moving away from short, densely connected networks to more widespread networks. These new networks properties require increased effort and energy, potentially increasing the vulnerability of the brain to a secondary injury.

1.5 Summary Of Changes In Brain And Behaviour Following Concussion.

Concussion is often viewed through the reported cognitive and physical symptoms that present following the injury and often recover within 7 – 10 days. The injury is much more complex and causes a series of cognitive, behavioural, neurometabolic changes, and alterations to the connectivity of the brain. Cognitively, SRCs most commonly cause impaired memory and verbal fluency, with a wide range of other cognitive processes often affected. The connectivity changes within the brain show the frontal brain regions to be more sensitive to injury following SRC. Accurate understanding of the various impacts concussion and SRC have on the brain is critical for the development of effective treatment and management plans.

1.6 SRC Management

Following sport-related concussions, the current guidelines for recovery include rest until acute symptoms resolve [30]. However, there is debate in the literature regarding the length of rest for optimal recovery. A recent study by Thomas and colleagues (2015) found that strict rest following concussion had no benefit and led to increased number of symptoms and delayed resolution [31]. Current recommendations are that individuals should rest for 3 days prior to a gradual return to pre-injury activities [32]. A review by Brolinson (2014) attempted to assess the evidence available for management of sports-related concussion and concluded that the evidence was so poor that they could not form a conclusion in regard to the benefit of rest, or exercise in improving recovery [33]. While optimal management of SRC is still in need of study there is reliable evidence supporting the implementation of a graduated return to play protocol.

1.7 Return To Play Protocol

The return to activity and sport following a SRC has been regulated through the return-to-play (RTP) protocol, originally created by the Concussion in Sport Group [34] and widely adopted, both in the following consensus statements and in practice around the world. Safe RTP is of critical importance due to the potential risk of both short-term [35, 36] and long-term damage [37]. The graduated RTP protocol consists of six progressive stages of incremental tasks related to sport performance (Table 1 – 1). The protocol begins with no activity during the recovery stage, followed by light aerobic exercise and gradually progresses to sport specific activities. Following each stage, the athlete is assessed for concussion symptoms, if none reappear; they are permitted to move to the next stage. Upon completion of the six stages and receiving medical clearance, the athlete is deemed ready to return to play. The current RTP protocol relies heavily on subjective symptom reporting.

Table 1 – 1 Example of the graduate return to play protocol for concussion recovery

Rehabilitation Stage	**Objective of Stage**
No Activity	Recovery
Light aerobic exercise	Increase heart rate
Sport-specific exercise	Add movement
Non-contact training drills	Exercise, coordination and cognitive load
Full-contact practice	Restore athlete's confidence; coaching staff assesses functional skills
Return to play	

The RTP protocol relies on subjective symptom reporting, using the post-concussion scale (PCS). While the PCS has been shown to be reliable [38], the validity of using symptoms is highly questionable as concussed athletes presenting with no symptoms continued to show deficits in neurocognitive testing [11]. In addition, athletes are known to underreport symptoms in order to return to play [39], decreasing the validity the testing. Furthermore, concussion assessments often occur immediately following the incident or the stage of exercise, this is critical, as the literature shows that exercise can result in post concussion-like symptoms in healthy individuals [40-42]. There remains a need for an objective measure to reliably track concussion recovery and provide accurate assessment of brain recovery within the return to play protocol. The results from this thesis provide preliminary objective measures of healthy brain activity in healthy young adults during graded exercise and cognitive tasks. These results can be used in future studies to determine changes in individuals recovering from concussion.

1.8 Effect Of Cognition And Exercise On SRC Recovery

Sports are a complex combination of physical activity and cognitive function. Therefore when testing for recovery, both exercise and cognition should be assessed. Lee and colleagues (2015) incorporated a cognitive task into a standardized exercise protocol in order to investigate if this would provoke a greater number or severity of symptoms in healthy individuals [40]. Although no increase in symptom reporting was reported with the addition of the cognitive task, the researchers noted that changes in exercise intensity and cognitive task difficulty could influence these results. When recently concussed athletes were tested following exercise, a significant difference was found in neurocognitive testing. McGrath and colleagues (2013) had athletes who were asymptomatic at rest and returned to baseline on the ImPACT (a commercially available neurocognitive test) complete an exercise session and repeat the neurocognitive testing. They found 27.7% of athletes showed a post-exertion decline in neurocognitive function that was not attribute to overall performance but specifically in memory ability [43].

The introduction and application of objective measures such as EEG is critical for the continuation to develop the understanding of the concussed brain and the recovery process. Advancements in EEG software and hardware has allowed for recording of brain activity during more strenuous exercise. This provides an exciting opportunity to identify neurophysiological underpinnings of the brain involved during exercise and cognition, with the goal of potentially discovering new biomarkers of concussion. In order to accurately characterize the concussed and recovering brain, it is imperative to first fully understand how the healthy brain is influenced by cognition and exercise.

1.9 Purpose Of Thesis

When the brain is injured or in a vulnerable state such as following a SRC, the brain will react differently as it completes the tasks. Understanding the neurophysiological impact of load on the healthy brain is of critical importance as it can then be used as a baseline for pathological populations. This thesis set out to explore and identify the characteristics of the healthy brains response to multi modal loading.

1.10 Objective And Aims

The objective of the current study was to examine the association between EEG metrics and behavioural changes in healthy normal adults as a foundation for evaluating individuals with concussion.

The aims of this study are:

1. To evaluate the association between EEG power and functional connectivity metrics and performance during cognitive loading.

2. To evaluate the association between EEG power and performance during physical loading.

3. To evaluate the association between EEG power and functional connectivity metrics and performance during a combination of cognitive and physical loading.

4. To compare EEG power and functional connectivity metrics between the types of loading.

1.11 Hypotheses

1. Increased cognitive load will result in a decrease in task accuracy.
2. Cognitive load will result in significantly increased power in all frequency bands.
3. A positive load dependent relationship will emerge between the working memory task and local connectivity measures (degree, clustering coefficient, betweenness) within the frontal brain regions.
4. The combined cognitive – exercise task will be associated with a significantly greater increase in frontal activity than either task individually.

In Chapter 2, I cover the basics of EEG and the traditional methods of analysis, followed by detailed explanation of the analyses incorporated in this work. This includes source analysis, power spectrum analysis, and functional connectivity through graph theoretical analysis. In Chapter 3, there is a literature review exploring the current understanding of cognitive, physical and combined loading and it's affect on behaviour and neurophysiological measures. The methods of my study will be discussed in Chapter 4, detailing the study design, data analysis techniques used, and the statistical analyses.

In order to understand how the healthy brain is affected by multi-modal loading, I present the findings of my research in Chapter 5, which utilized a repeated measure design to compare brain activation during a cognitive task, an exercise task, and a combined cognitive-exercise task. Thirteen healthy young participants (22.5 years old ± 0.65) completed the three tasks on three separate days in a randomized order. During all conditions, brain activity was collected through EEG, along with behavioural measures. This adds to the current literature on the effect cognition, exercise and a combination of the two influence the neurophysiological features of the brain and provides healthy control data for future studies to assess individuals recovering from SRC.

Chapter 2: Basic Principles Of EEG And Analysis

2.1 What Is EEG?

Electroencephalography (EEG) has been used to measure human brain signal for almost a century. Discovered by Hans Berger in 1924, the German psychiatrist was able to successfully measure brain activity in humans during various states including: sleep, wakefulness, and focused attention [44]. EEG is a graphic representation of voltage changes between two cortical locations plotted over time [45]. The voltage changes, or signal, are the postsynaptic potentials of the cortical neurons. Or in other terms, the EEG measures voltage changes on the skull at all electrodes [46]. The electrical potential of a single neuron is much too small to be recorded through EEG and therefore in order to be measured, a large group of neurons (i.e. 10^7 neurons [47]) must activate simultaneously to produce a strong enough signal. The electrical potentials created by neurons also form an electric field. When large groups of neurons activate simultaneously the sum of the activity creates a local field potential. Local field potentials (LFPs) can be open or closed depending on their orientation. Open LFPs are orientated perpendicular to the scalp while Closed LFPs run parallel, as such surface EEG is only capable of measuring Open LFPs [48].

All regions of the brain produce local field potentials, however due to the layers that surround the brain: the cerebrospinal fluid (CSF), the skull, and the scalp; the signal is greatly attenuated by the time it reaches the surface [44]. The main source of EEG signal originates from the cerebral cortex, as a limitation of EEG is its inability to measure deeper cortical structures. While the EEG has low spatial resolution, it is one of the only neuroimaging techniques with sufficient temporal resolution to record the fast dynamic changes of cortical activity. EEG can be recorded between 250 and 2000 Hz or samples per second.

2.2 Traditional EEG Analysis

Early studies using EEG aimed to examine the raw signal to identify changes due to a specific task or stimuli. As the technique advanced, studies began taking advantage of averaging the signal. This led to the development of the event-related potential (ERP) technique and became the primary analysis of EEG in cognitive neuroscience. ERPs are time-locked to a specific stimulus and as such have allowed for the observation of many specific aspects of cognitive function including task preparation, stimuli identification and cognitive function [46]. The ERP waveform is composed of peaks and dips that allow for the visualization of neural processing throughout the trial (Figure 2-1). The peaks and dips of the ERP are known as components and are defined by their polarity (negative or positive), timing, scalp distribution and sensitivity to task changes [46].

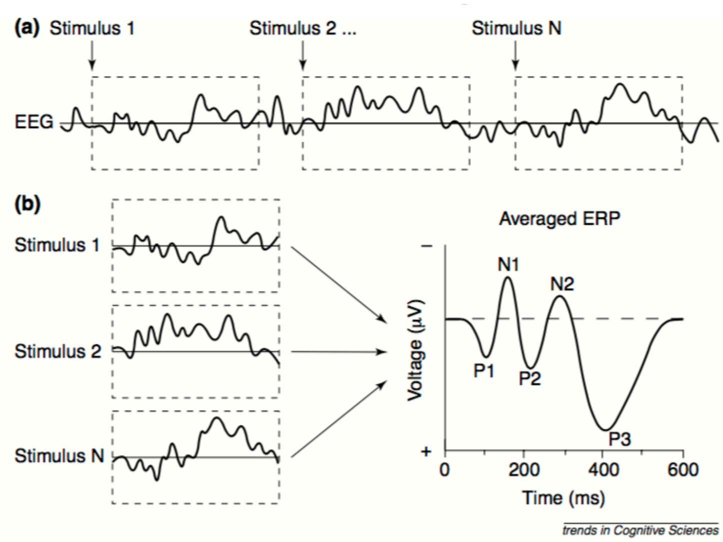

Fig. I. Extraction of the ERP waveform from the ongoing EEG. (a) Stimuli (1... N) are presented while the EEG is being recorded, but the specific response to each stimulus is too small to be seen in the much larger EEG. **(b)** To isolate the ERP from the ongoing EEG, the EEG segments following each stimulus are extracted and averaged together to create the averaged ERP waveform.

Figure 2 – 1. Example of how an average ERP waveform is created.

Over the years many components of the waveform have been identified and attributed to specific functions. For example, P1 and N1 are indicative of information processing in the visual cortex and perceptual analysis, respectively [49, 50]. Further along the waveform is another component known as P3, which is attributed to working memory encoding and maintenance. Advances in EEG methodology have made it possible to record brain activity from a large number of electrodes over the entire head. This had led to very dense ERP data sets that can be cumbersome and difficult to interpret. New analysis techniques have emerged to discern additional information not fully reflected within the ERP waveforms.

2.3 Source Analysis

The LFPs mentioned above are in the form of dipoles, with both positive and negative charges. An important aspect of EEG is the location, strength and orientation of the dipoles as these measures can greatly influence the recorded signal. For example in Figure 2-2 a single dipole is shown near the central electrode (Cz). On the left, the dipole is orientated towards the scalp and this is where the max activity will be found. On the right, the dipole is orientated tangential to the scalp. This results in a change of the signal and almost no activity is present above the dipole.

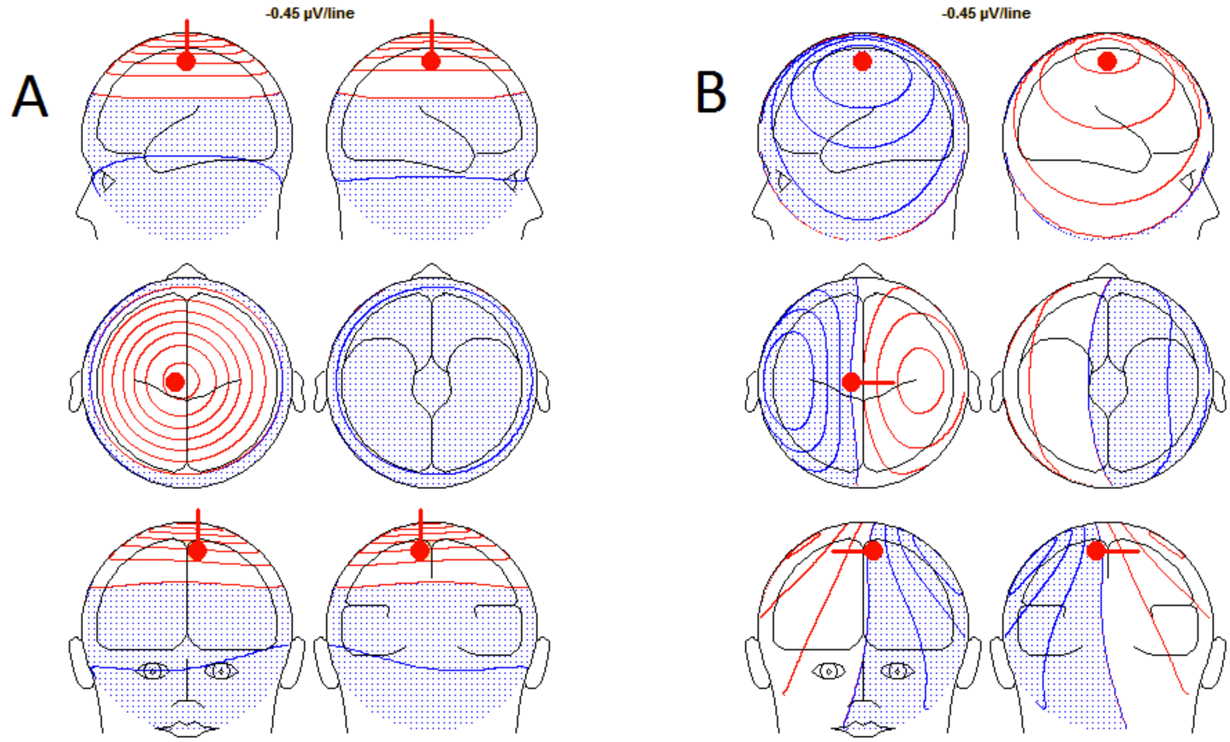

Figure 2 – 2 Example of the effect orientation has on a single dipole positioned at electrode position Cz [48].

The influence of dipole orientation and the effect on EEG activity stresses the importance of understanding the cortical source of EEG activity, which is one of the major limitations with using EEG. Therefore extensive work has been done in attempts to develop methods capable of localizing the activity to a particular cortical source. There are two methods used to approach this issue: (1) investigate which cortical region is responsible for the recorded EEG signal, or (2) investigate how particular brain regions contribute to the recorded brain activity. The first method is addressed through source localization being applied to the signal to determine the location of the dipoles. Source localization is a signal processing technique that takes the voltage potentials at the various scalp locations and estimates the current sources inside the brain that best fit this data [51]. This requires solving the inverse problem. That is, each electrical potential measured at the scalp can be explained by activity of an infinite number of cortical configurations. This problem can only be solved by applying multiple *a priori* assumptions regarding the generation of the EEG signal [52]. Many source localization algorithms exist, each attempting to optimally explain the scalp activity by cortical sources.

An alternative method in understanding the cortical source of the scalp activity is through the application of source montages, a type of virtual montage. This digital EEG reconstruction calculates the topography of the signal using all the recorded electrodes. The signal is then reconstructed at each recorded electrode site as well as any ‘virtual’ electrode located on the scalp. This allows for the construction of standard EEG montages such as the reference free, 10-10 and 10-20 systems (Figure 2-3).

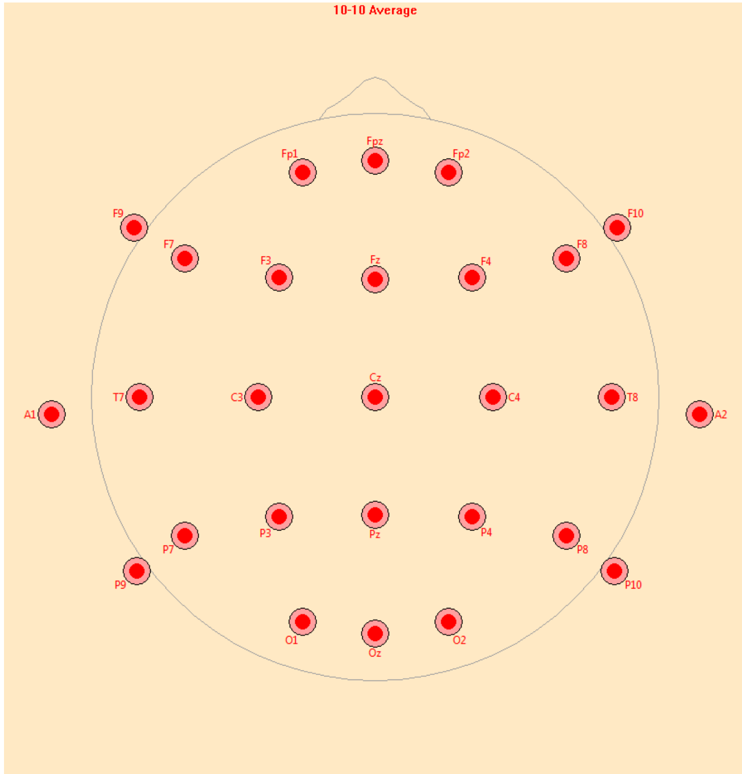

Figure 2 – 3 Virtual electrode placement in 10-10 Average montage.

Virtual montages are excellent at recording radial activity underneath each electrode, but have shown to be less sensitive to tangential activity and require the addition of whole-head spherical spline maps to reflect cortical source activity [53]. Once a source montage is applied the resulting traces can be viewed as large virtual electrodes that are roughly 3-4 cm in diameter placed on the cortical area it is supposed to be modeling. Source montages reconstruct approximate source waveforms, which are calculated using the generalized montage, previous knowledge on scalp topographies results from the EEG recording, and linear algebra. For a more detailed description of the creation of source montages refer to the review by Scherg and colleagues [53]. These source waveforms are an estimate of the magnitude of the activity of each region over time and allow for a simple representation of the cortical activity. The source montage used in this thesis consisted of 15 sources created to best estimate cortical activity of the entire brain (Figure 2 – 4).

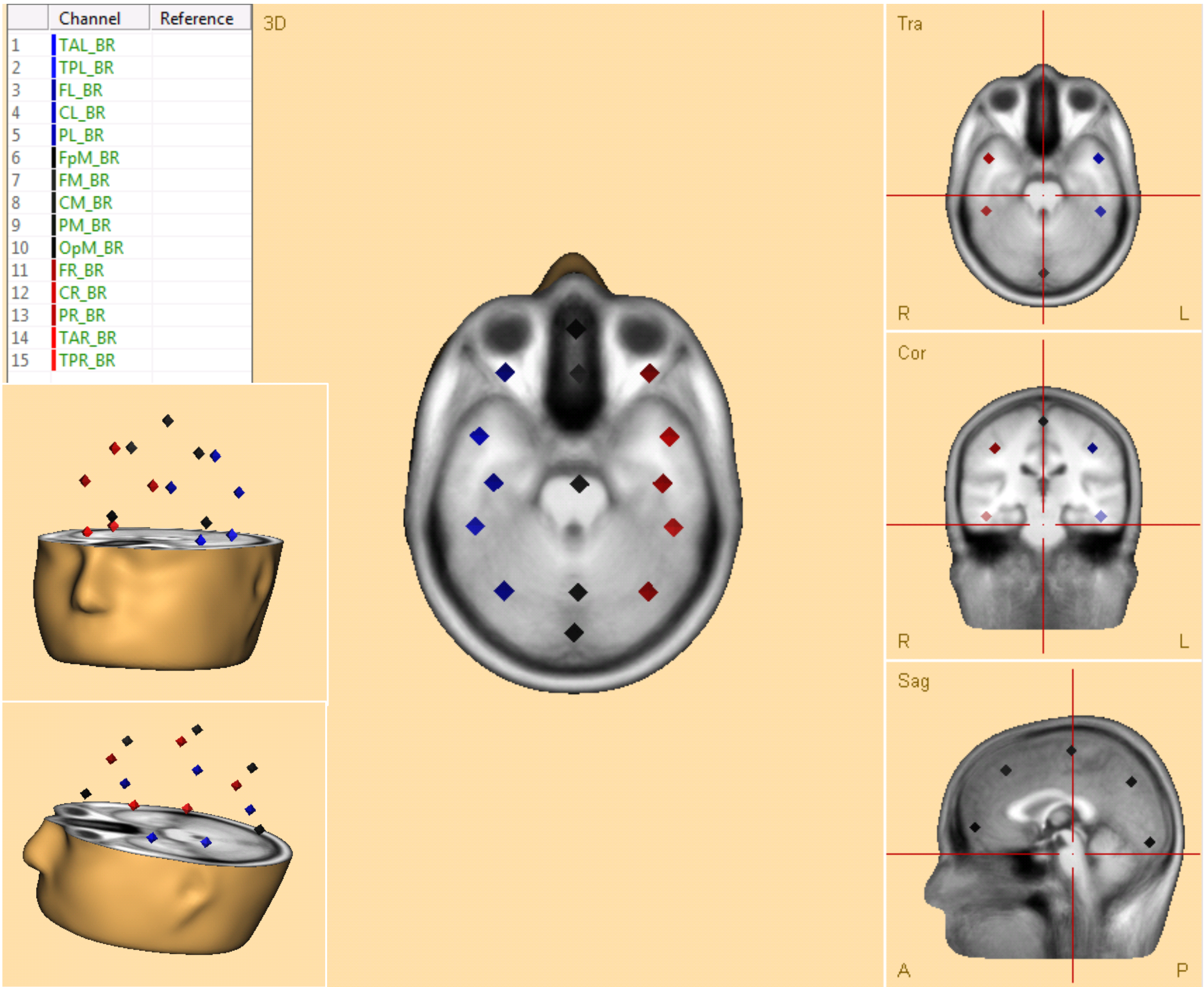

Figure 2 – 4 Location of Sources in the Virtual Source Montage. Transverse, Coronal and Sagittal 2D views and 3D views for better visualization of region distribution.

2.4 Power Spectrum Analysis

In order to understand EEG signals, interest has developed in analyzing specific frequency bands, as they have been shown to represent specific neurological processes [54]. When recorded from the scalp, the EEG signal is the culmination of all the frequency bands together. In order to assess the individual frequency bands, a fast Fourier transform (FFT) is used. The algorithm works by taking the EEG data, collected in the time domain, and transforms it into the frequency domain allowing for the frequency bands to be divided for separate analysis. The FFT is an algorithm that rapidly converts a signal from the time domain into a representation in the frequency domain using the discrete Fourier transform (DFT). The DFT creates a voltage by frequency spectral graph known as a "power spectrum", where power is equal to EEG magnitude squared. EEG power represents the distribution of signal power over frequency and has been reliably shown to relate to cortical activity. When combined with blood oxygen level-dependent (BOLD) signal in fMRI, results show a frequency dependent relationship with low frequency EEG being negatively correlated and higher frequencies being positively correlated [55, 56].

2.4.1 EEG Frequency Bands

Following the FFT, the EEG signal is transformed from a single signal into multiple signals with various frequencies. The EEG signal is commonly composed of frequencies between 1 – 50 Hz. The frequencies are grouped into the following 5 bands ranging from slow (delta) to fast (gamma).

- Delta (0.5 – 3.5 Hz): Composed of the slowest frequencies, delta waves are the dominant frequency during early developmental stages [57], and sleep in adults [54]. In addition, delta is associated with learning, motivation and the brain reward system [58]. In terms of cognition, delta found to be linked to the P3 ERP component in various cognitive tasks. This connection is theorized to be related to motivation, with delta activity seeming to help motivate the brain to pay attention to the stimuli for task completion [58].

- Theta (3.5 – 7.5 Hz): Associated with working memory and inhibitory control. Theta and particularly in frontal midline is thought to have an active role in the maintenance phase of memory [58, 59], which coincides with its recorded connection to the hippocampus [60].
- Alpha (7.5 – 12.5 Hz): Appear spontaneously during wakefulness, relaxed states and mental inactivity or resting state. Most pronounced within the occipital lobe during eyes closed conditions [54], while also linked to working memory and short-term memory functions [61].
- Beta (12.5 – 30 Hz): Historically linked to motor functions, more recent research suggests beta frequency involved in maintaining the status quo within the sensorimotor system [62]. Further studies have indicated elevated beta activity during the delay phase in working memory tasks [63].
- Gamma (30 – 60 Hz): Highest frequency band shown to be involved in wide variety of actions including stimulus selection, attention, arousal, object recognition, memory formation [64, 65]. Gamma activity often found to be locked with slower frequencies indicating a potential interaction required for proper memory function [65].

Cognitive functions involve oscillations from multiple frequency bands as many brain regions must interact and communicate for successful functioning. Oscillations of different frequencies are indicative of global state changes in the brain [62]. Higher frequency oscillations are indicative of arousal and more distinct activation patterns, whereas low frequency waves are present in of low arousal and global state changes.

2.4.2 External Factors

The various frequency bands have well identified cognitive functions and are often used to assess cortical activity in response to a particular task. When there is an increase in a specific frequency it is interpreted to be the result of the task. It is important to note that there are several external factors that can influence cortical activity as measured through EEG. Drugs can have a large influence on EEG activity that can confound results and cause in accurate interpretation if not taken into account. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have shown to significantly impact frontal theta power, alpha and beta frequencies [66]. Antipsychotic drugs, such as Clozapine, have been linked to increased delta and theta power in frontal brain regions as well as decreased alpha and beta. Mood stabilizers have shown to lead to increased delta and theta wave activity, decreased alpha activity and varying effects on beta depending on the medication. Stimulants, such as caffeine, are shown to acutely increase attention, alertness, and restore performance due to fatigue [67]. However, studies show caffeine to lead to a significant decrease in EEG power across the spectrum in fronto-parieto-occipital and central electrodes [68].

Other common external factors that can influence EEG activity include depression, anxiety, and attention-deficit hyperactivity disorder (ADHD). Depression has been shown to cause significant increase in absolute beta power, in addition to an overall shift to faster frequencies across the spectrum [69]. Meanwhile, anxiety is linked to an increase in global alpha power in both males and females [70]. ADHD, a neurodevelopmental disorder, has been shown to cause an increase in theta power and decrease in beta power when compared to controls [71]. These changes that result form medication, or neurological disorders stress the importance of proper screening and identification of potential factors that can influence EEG signal. This ensures that the interpretations of the resulting changes in EEG are in response to the task and not from any other cause.

2.5 Functional Connectivity

The ability of the human brain for higher cognitive function is theorized to be the result of structural and functional connections forming complex networks between widespread brain regions. These networks have been proposed to represent the physiological basis for information processing and mental representation [72-74]. A variety of methods and imaging modalities have been used to characterize the many structural and functional networks that allow for the integration and segregation required for information processing[75]. Graph theoretical analysis (or Graph theory) is an analysis technique that allows for noninvasive mapping of these structural and functional networks and their properties. It begins by modeling the brain as a series of complex networks and identifies the many topological properties of these brain networks [75]. Both structural and functional brain networks can be constructed using the following four steps provided by Bullmore and Sporns [76] (see Figure 2 - 5.):

1. Define the nodes of the network. These can be defined by electroencephalography electrodes or alternatively as anatomically defined regions (MRI, DTI).
2. Estimate a continuous measure of association between nodes. This is possible through a variety of ways, including spectral coherence, Granger causality or through conditional dependence and independence between any two regions based on all other brain regions.
3. Generate association matrix by calculating all pairwise associations between nodes and apply a threshold each element to produce a binary adjacency matrix. This matrix is composed of the number of edges between each pair of nodes. In most cases, this is binary, 1 (edge present) or 0 (no edge between nodes).

4. Calculate network parameters of interest for this graphical model of brain network and proceed to compare against a series of random networks with the same number of nodes.

A network in graph theory is stated to be composed of a series of nodes and edges. The topological properties of these networks can be defined by a variety of measures. While not exhaustive, below is a list of measures commonly applied to explain structural and functional brain networks:

Node Degree

A critical measure for the network, degree represents the number of connections or edges each particular node has. Individual node degree denotes the importance of the node to the network. Degree is also a measure centrality, in that a node with high degree interacts with many other nodes in the network [74].

Clustering Coefficient

Another important measure of connectivity, if a node's nearest neighbors are also connected to each other, the graph forms a cluster. Clustering coefficient represents the local connectivity of a graph. Small-world networks, like the brain, have high clustering and small path lengths [77].

Path Length And Efficiency

Path length is the minimum number of edges needed to go from one node to another and represents the level of global integration of the network. The average shortest path of a network is the average of all shortest paths between all pairs of nodes. Global efficiency is the inverse of the average shortest path. Local efficiency of an individual node is the inverse of the average shortest path connecting to that node. Global and local efficiency measure the ability of a network to transmit information at the global and local levels [76-78].

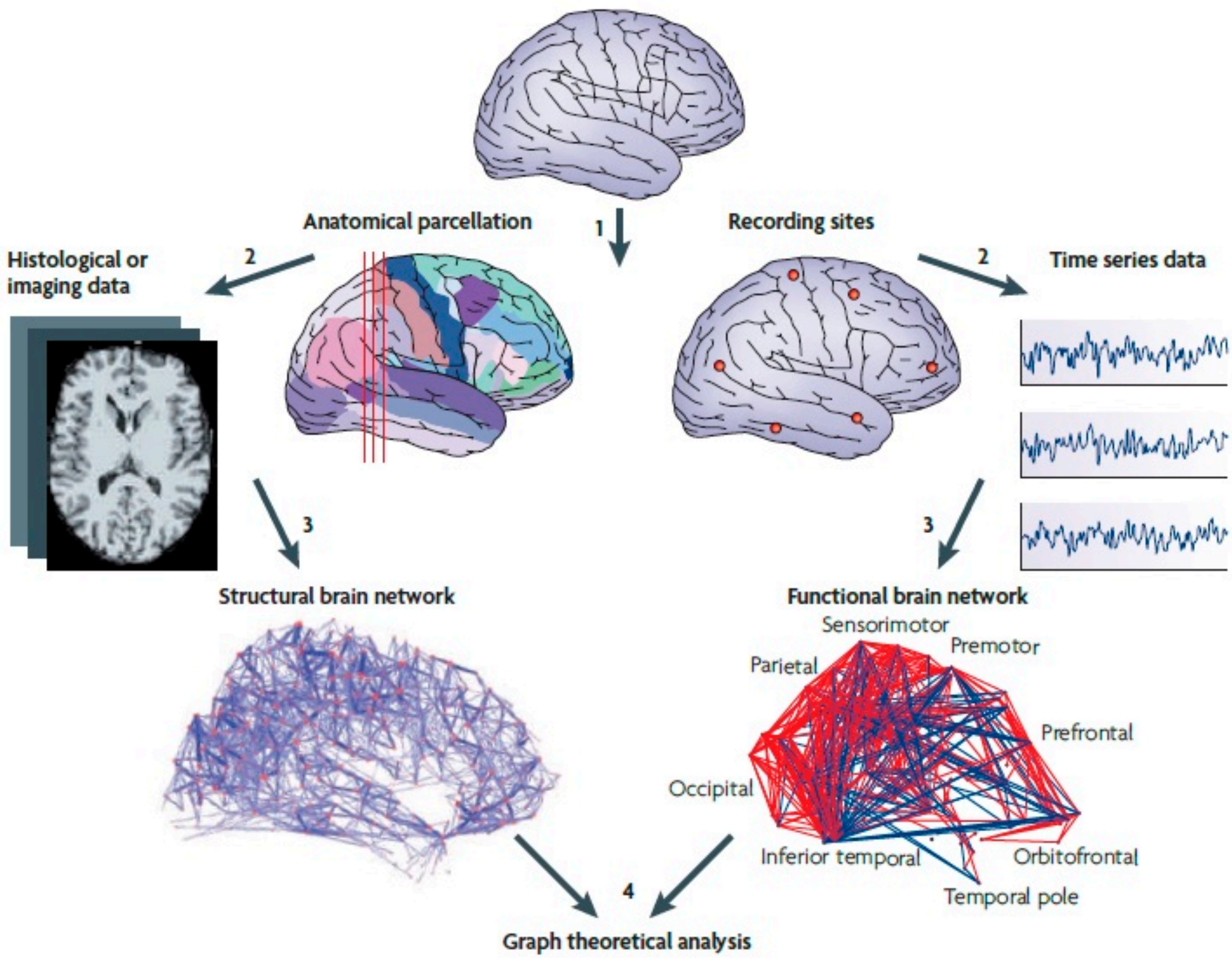

Figure 2 - 5. Representation of process to create structural and functional connectivity networks using graph theoretical analysis.

Modularity

Modularity is a measure of structural networks tendency to form modules. Modules are a group of nodes that are strongly connected to each other but not to other nodes. Modules play an important role in complex networks as they often have different functional roles within the network [76, 77].

Centrality And Hubs

Centrality is a measure of how many shortest paths between other nodes pass through a particular node. High centrality reflects that nodes importance to the network. A hub is a node with high degree or centrality. If considered in conjunction with modularity, there are two types of hubs: provincial (hubs connected to vertices in the same module) and connector hubs (hubs connected to nodes in other modules) [76, 77] (See Figure 2 - 6).

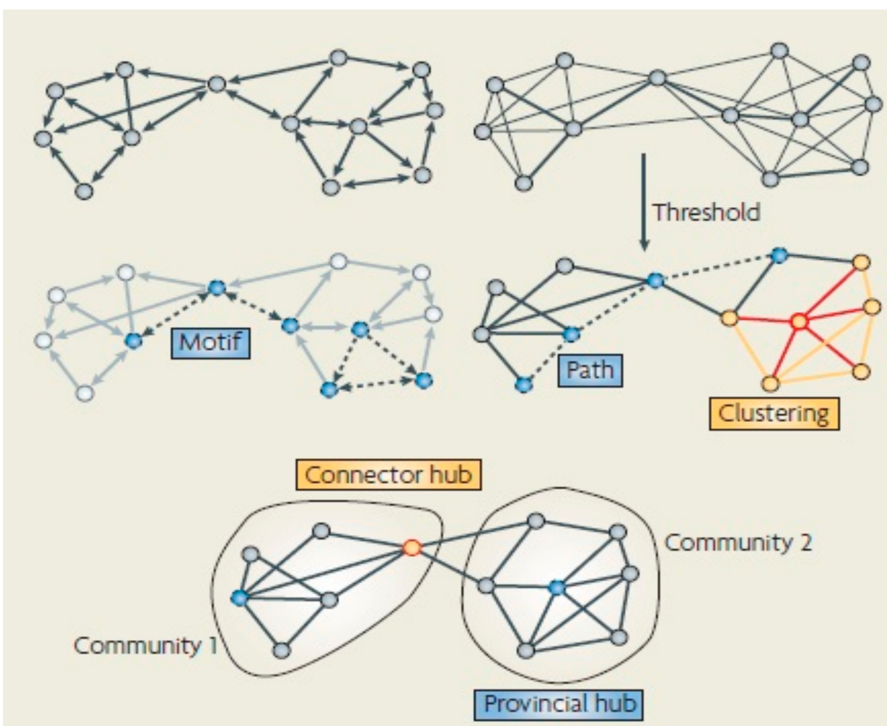

Figure 2 - 6. Graphical representation of network measures.

By utilizing graph theoretical analysis of brain connectivity it is possible to get a complete and thorough description of the structural and functional networks within the brain, providing critical information for both research and clinical applications.

Chapter 3 Literature Review Of Cognitive Function And Exercise

3.1 Cognitive Function

Executive function (EF) is a general term that includes task switching, planning, attention, working memory, and inhibitory control among others. The prefrontal cortex (PFC) is known to play a crucial role in all executive function processes, however the PFC is a heterogeneous neuro-anatomical region and different areas have been proposed to be responsible for separate cognitive functions [79]. The DLPFC, ventrolateral PFC (VLPFC) and ACC have all been identified as regions involved in two sub-processes of EF: response inhibition and working memory.

The ability to inhibit external distracting stimuli and focus on a specific task is a crucial component of everyday life and an important component of executive function. Common inhibitory control tasks include the Stroop task, the trail making test, and the anti-saccade task. The anti-saccade task [80] has been used extensively to examine visual attention, reflexive inhibition, and neurophysiological status [81]. This task involves looking away from a peripheral target by suppressing the automatic response to look at the target and then create a voluntary motor command to look away [82]. The task requires input from many subcortical structures, including the pontine and midbrain nuclei, as well as cortical structures such as the PFC and ACC [83, 84].

Working memory (WM) is a term that describes a cognitive function that can hold and manipulate information within the brain for a limited amount of time, for the purpose of a specific cognitive activity or task. It also includes sustained attention and focus on particular information, while rejecting distractors [85]. WM is required for complex cognitive tasks such as comprehension, reasoning, planning, learning and mental arithmetic [86, 87]. Baddeley and Hitch [88] first defined working memory in 1974, wherein they proposed a multicomponent model that had separate verbal and visual systems, under the control of a central executive. Extensive animal and human studies have demonstrated that the prefrontal cortex (PFC) is a key area involved in working memory [86]. In particular, the DLPFC, VLPFC and ACC [89] have been associated with working memory. Their specific roles are still debated but the DLPFC and ACC are active during retention of information. ACC activity also seems to be particularly influenced by task difficulty [90, 91].

3.1.1 EEG Measures Of Cognitive Function

Neuroimaging is critical to understanding the brain regions involved in EF and its sub-processes. EEG is sensitive to changes in brain activation at rest and during cognitive tasks. As a non-intrusive imaging modality with high temporal resolution, EEG is an optimal neuroimaging modality to study EF. Findings with EEG suggest the presence of a load effect, wherein increasing cognitive load through working memory task difficulty, elicits a greater response in brain activity in frontal brain regions [55, 92-95]. However, this finding has shown to be frequency dependent as well as location specific.

Frequency of the EEG oscillations are important as they can control the timing of neuronal firing and coordinate information transfer between different brain regions [62]. This study focused on theta, alpha, beta, and gamma frequency bands as these have shown to be particularly sensitive to working memory and exercise.

Theta activity has been reliably shown to have a major role in working memory [95]. In particular, theta activity has been linked to encoding and retention of information. Multiple studies incorporated a modified Sternberg task to test working memory and theta activity. These studies found with increasing WM load there was a corresponding increase in frontal midline (FM) theta activity [55, 93, 94]. Maurer and colleagues also found that the increase in FM theta was correlated with accuracy: the larger the increase in theta, the greater the decrease in accuracy [93]. This effect is not task specific as Ku and colleagues found similar relationship with FM Theta using both a visual and auditory mental addition task [92]. Through the application of intracranial EEG and source localization, the medial PFC and ACC have been identified as the cortical origin of the FM theta activity [91, 93, 96].

Activity in the alpha frequency band has traditionally been linked to steady state or idling activity with amplitude suppressed by eye opening and visual stimuli. Recently, high resting alpha power has been linked to increased WM performance as well as successful saccadic control [84]. Alpha is suggested to play an important role in saccadic control network circuits and top-down control of suppressing external saccades [84]. Other studies show alpha power involved in working memory and mental arithmetic [92] suggesting that alpha is an active contributor in attention and consciousness. During WM tasks, alpha activity is reduced and negatively correlated with cognitive load [93, 97, 98]. The alpha frequency is often separated into low (8-10 Hz) and high (10-13 Hz) bands due to their varying sources of origin and activity. Low alpha is found over parietal, temporal and superior frontal regions and is shown to be more sensitive to load and decreases with increasing WM load [93, 98, 99]. High alpha on the other hand originates from occipital and occipital-parietal regions and is sensitive to visuospatial factors, and to a lesser extent cognitive load [85, 93]. Successful WM performance is also linked to high resting alpha power, which is thought to correlate with successful saccadic performance.

Activity in beta has been linked to a variety of cognitive processes including movement related, sensory, cognitive and emotional stimuli. Studies have identified its role in sensorimotor functions [62] and been associated with sensory processing [100]. For WM performance, there have been mixed findings as some studies show increased beta activity while others show a decrease [101, 102]. Guntekin and colleagues (2013) identified the presence of a physical response to be the cause of the result variations. When no physical response is required, beta power increases during WM tasks and is sensitive to cognitive load [103].

Gamma activity has been linked to a wide range of cognitive processes including movement preparation, attention, sensorimotor integration and memory formation [62]. A critical component of WM is the maintenance phase, where the stimulus is no longer present and the information must be temporarily stored prior to the required manipulation to complete the task. Increased gamma synchronization has been reported during attention and maintenance phase of WM [104]. Gamma activation found to be partially location specific, depending on the type of cognitive task. Auditory processing regions such as the putative auditory dorsal and ventral processing streams found to have increased gamma activation following auditory WM tasks [104, 105]. Visual WM tasks such as the delayed-matching-to-sample task used by Tallon-Baudry and colleagues [106], caused increased gamma activation at occipital and temporal EEG electrodes during the maintenance phase. Gamma activation is also shown to be linearly correlated with WM load [107].

WM requires well-organized communication between various brain regions. This communication occurs along the WM networks where groups of neurons activate at the same frequency cycle. By measuring the connectivity of the network it is possible to determine how distant brain regions cooperate and transmit information [108]. Various neuroimaging modalities have been used to identify WM networks, regions that are activated during visual WM tasks, composed of frontal, temporal, parietal and occipital lobes. When assessing neuronal interaction and communication, oscillatory phase synchrony is important as each frequency band can have a specific role [109]. Payne and Kounios used a Sternberg Recognition task and found an increase in theta coherence between frontal midline and temporal-parietal regions and alpha coherence in midline parietal and left temporal-parietal [110]. Furthermore, a MEG/EEG study found inter-area phase synchrony was strengthened with increase WM load, particularly in fronto-parietal regions in alpha, beta and gamma bands [111]. Using graph theoretical analysis, visual WM networks have been described, indicating connection density to be load dependent in alpha (10-13 Hz), beta (18-24 Hz) and gamma (30-40 Hz) within the fronto-parietal and visual areas [112]. Other graph theory components can provide more information about the visual WM functional networks. Clustering coefficient and path lengths have been found to be WM load dependent. Li and colleagues (2011) showed variance in changes depending on the hemisphere of the task. Clustering coefficient significantly increased with load in alpha, beta and gamma bands in the left visual field and all the bands in the right visual field. Path length was also influenced by load but in fewer frequency bands (Left: theta, beta and gamma; Right: beta). These results suggest that WM load changes the local connectedness of the brain networks [113].

Recently, Zhang and colleagues (2016) found load dependent connectivity changes in theta along frontal midline areas. The curve of the connection strength increased from loads 1 – 4 before decreasing. The accuracy of the task also decreased with load [108]. This data supports the concept of WM capacity, which is the amount of information that can be temporarily stored and manipulated. Behavioural studies have suggested that WM has a capacity of holding up to four items before faltering [114, 115]. The connectivity results suggest that once WM exceeds capacity there is a decrease in efficiency and activity within the WM network that leads to a decrease in accuracy.

3.2 The Brain And Exercise

Exercise is known have many health benefits including improved cognitive learning, executive function and even protection from age related decline [116]. Through animal models, the mechanisms responsible for these benefits have been studied extensively. They include: improved plasticity and neurogenesis within the hippocampus (particularly the dentate gyrus [117]) and increased levels of synaptic proteins [118] and glutamate receptors (NR2b and GluR5) [119]. Exercise is also responsible for increased availability of growth factors, such as brain derived neurotrophic factor (BDNF) and insulin growth factor 1 (IGF-1) [120, 121]. Exercise also contains neuroprotective properties aiding in both recovery and reducing the severity of many types of injuries and illnesses including depression [116]. These benefits have primarily been reported as a result of exercise sustained over an extended period of time (3-12 months) [122-125]. While research has shown benefits from acute exercise, these studies primarily focus on immediately following exercise completion and not during the exercise session. The specific influences exerted on the frontal brain regions during acute exercise remain to be fully explored.

Motor skills such as those involved in sport participation, require the integration of information from a wide range of areas including peripheral sensors, spinal locomotor networks as well as motor and premotor cortices [126]. Due to the temporal resolution that EEG provides, it is possible to study the neural control of movement. As mentioned above, by studying the oscillatory components of the EEG signal, it is possible to investigate neuronal interactions and communications. With exercise, theta, alpha, beta and low gamma frequencies have shown to be of interest and reflect different aspects of motor planning, execution and control [127, 128].

During sport specific activities, increases in frontal midline theta power was linked to improved performance in expert golfers [129] , and rifle shooters [130]. The source of theta FM has been localized to the medial frontal cortex and the ACC, areas important for focused attention. Furthermore, along with playing a major role in cognition, learning, and memory; theta oscillations have been proposed to be involved in the integration of sensory and motor information during sensorimotor actions [131]. A recent study by Cruikshank (2012) found increased theta power during a sensorimotor task in motor areas (C3 and C4) [132]. Similarly, theta power was found to increase during movement onset of upper limb ballistic movements in contralateral motor cortices [133].

During and immediately following large body movement such as treadmill walking and cycling, studies have shown EEG activity to increase across frequency ranges [134, 135]. Bailey and colleagues (2008) found increased activity across EEG frequencies, including theta, during a graded cycling session to fatigue. This increase in activity was shown to occur at multiple electrode sites, leading the authors to question if peripheral physiology was the driver of the EEG activity [135]. Alpha activity in response to exercise has been difficult to quantify reliably, as studies show both increased power [135, 136] and decreased power [126, 137]. An important distinction to take under consideration is the time of cortical recording in relation to the exercise.

Kubitz & Mott (1996) recorded EEG during a 15-minute (three 5-minute stages) session of progressively more intense exercise (50 to approximately 150 W) on a cycle ergometer. They found an exercise related decrease in alpha activity and corresponding increase in Beta activity over baseline values at each exercise load. The activity returned to baseline after completion of the exercise [137]. More recently, Enders and colleagues recorded EEG during high intensity cycling and found increase in alpha, beta and gamma activity over the left frontal cortex. This increase in activity corresponded with fatigue, specifically for the alpha and beta frequency bands. The gamma activity was unchanged with fatigue. They proposed that their results indicate involvement of the cerebral cortex during cycling in an executive control and motor planning capacity.

When cortical activity is measured following exercise completion there is a similar activation pattern [126], however, the frequency band and region of activation is dependent on exercise type and familiarity with the modality. Brummer and colleagues (2011) had experienced runners perform treadmill running, cycling on an ergometer, arm crank, and isokinetic movement at 50% and 80% intensity and recorded EEG prior and following the exercise. Following moderate intensity exercise, alpha activity showed an increase with all exercise modalities, while beta increased over the parietal cortex during the bicycle trial only. In contrast, during high intensity exercise alpha activity had modality dependent changes. Cycling and hand crank resulted in no change in activity; treadmill running had decreased alpha activation and isokinetic trials showed increased alpha activity. Beta activity meanwhile showed a decrease in activation in frontal brain regions for the treadmill trial [138]. Another study meanwhile found increased absolute power in beta following a graded cycling test [139]. These results suggest that exercise type and intensity alters cortical activation and that the region of activation is related to participant familiarity with the modality.

A meta-analysis by Crabbe and Dishman (2004) assessed the literature on EEG changes during and immediately following exercise. They concluded that EEG activity in delta, theta, and beta frequencies increased both during and immediately following exercise. Activity in alpha showed changes in absolute power, but not in terms of relative power to the other frequencies. The authors also noted that the changes in activity were widespread and not grouped to specific cortical sites [134].

Few studies have attempted to assess the impact of acute exercise on functional connectivity measures. The sparse existing literature suggests that immediately following exercise there is an increase in functional connectivity in sensorimotor areas, while no impact has been reported in frontal regions [140].

3.3 Combining Cognition And Exercise

The incorporation of a cognitive task with the graduated exercise for the RTP protocol strives to increase the load on the brain in order to elicit symptoms from the post-concussed brain. The hypofrontality theory proposed by Dietrich (2003) suggests that during exercise there is a high level of activation within the motor and sensory cortexes which leads to a re-allocation of the limited resources normally needed for information processing [141]. This results in an inhibition of neural networks not involved in exercise. Therefore if an individual attempts to perform a task using the PFC, a brain region not heavily involved with exercise, it is much more difficult and requires increased effort. Davranche and McMorris (2009) assessed cognitive function during steady state cycling at individual lactate thresholds and found improvement in RT during trials of the Simon task but impaired function in response inhibition [142]. A similar study had participants cycling at 30%, 50% and 80% of their heart rate reserve (HRR) while performing the Wisconsin Card Sorting Test [143]. They found significant impairment in performance during high-intensity exercise but not moderate or low intensity [144]. They concluded that their results lent support for the hypofrontality theory. Recent meta-analyses on the effect of acute exercise on cognition found that exercise has a consistent positive effect on cognitive tasks completed following exercise completion [145, 146]. When cognition is assessed during exercise, the results are less conclusive. The variations in results were proposed to be methodological, as Chang and colleagues included a wider range of studies and participants, resulting in a small positive effect on cognition [145], whereas Lambourne and Tomporowski incorporated a narrow scope of studies, only including healthy young participants and a negative effect. The meta-analyses identified moderators that were found to influence the outcome of studies that included exercise intensity, time of cognitive testing and duration, cognitive task type, and fitness of participants. Following a meta-analysis on the effect of walking on cognition, Al-Yahya and colleagues found working memory and executive function tasks to be the most consistently and strongly influenced by exercise [147].

Neuroimaging provides an opportunity to understand the cortical origination of the changes in cognition with exercise. A study by Li and colleagues (2014) had participants complete an N-back test following rest and immediately following a 20-minute cycle at 60-70% HR Max. The authors found that behaviorally, the exercise did not influence the accuracy of the task but did have a significant effect on brain activation during the most difficult level of the N-back. Brain activation was increased in the right middle prefrontal gyrus, the right lingual gyrus, and left fusiform gyrus, areas involved in executive function. Decrease activation was noted in the anterior cingulate cortexes, left inferior frontal gyrus and the right paracentral lobule [148], which the authors implied was a transition to a default mode status and compensatory mechanism for executive processes.

EEG remains sparsely used for exploring cognition during exercise. One study had participants cycle at 60% of the HR max and found that as difficulty increased, in a modified flanker task, accuracy decreased and cortical activation increased [149]. Specifically, they found increased amplitude in the time-locked EEG signal in frontal brain regions. The authors suggested that the increased activation and decreased accuracy are indicative of increased inefficiency of the neuroelectric system. This leads to an increase in effort and resources to perform the task. Another, more recent paper by Olson and colleagues (2016) supported these results, as they reported a decrease in accuracy and corresponding increase in EEG activity at both 40% and 60% exercise intensity during a modified flanker task [150]. This increase in effort to complete the cognitive task was further supported by a study with adolescents that had participants exercise for 20 minutes at 60% of their HR max and complete a cognitive task composed of an Eriksen flanker task and Go No-Go task [151]. Using coherence analysis, which explores the synchrony of brain oscillations across different scalp locations, they found unfit adolescents showed increased coherence in Alpha and Beta frequencies. Increase coherence is suggested to represent increased effort. These results support two meta-analyses that identified fitness level to be a moderator that influences cognition during exercise [145, 146].

Overall, the results from the behavioural and neuroimaging studies support the theory of transient hypofrontality [141], in that with exercise there is a decrease in cognitive task accuracy and increase in cortical activity. This increase represents more resources being required to perform the task. The results from the neuroimaging studies suggest a decrease in neural efficiency during combined cognition and exercise. Graph theoretical analysis has the potential to provide more insight into how the various attributes of the functional networks are impacted by this paradigm design.

Chapter 4: Methods

The present study has received approval from UBC's Clinical Research Ethics Board (H15-02714). All participants independently provided written and verbal informed consent, in accordance with the principles outlined by the Declaration of Helsinki.

4.1 Participant Information

All interested participants were required to meet the following inclusion criteria:

- 18-25 years old
- Right handed
- No history of prior concussion or head injury
- No history of drug or alcohol abuse
- No diagnosis of learning disability or other neurological disorders;

In addition, interested individuals were screened over the phone using the Godin Leisure Questionnaire (see Appendix A). In order to participate, individuals had to be moderately active or a score of greater than 14 on the questionnaire. This was selected as familiarity with exercise and fitness level is known to influence the effect of exercise on cortical activity [145, 151].

All participants were recruited from the University of British Columbia and surrounding area through flyers (Appendix B) and word of mouth.

4.2 Anti-Saccade Serial Addition Task (ASAT)

The Anti-Saccade Serial Addition Task is a novel task that is comprised of two (2) well established tests: the Anti-Saccade Task and the Paced Serial Addition Task. The Anti-Saccade task is a classic test used to assess cognitive control and requires participants to inhibit a reflexive saccade [80]. The task is composed of two steps. First the participant must suppress the reflex to look at the stimulus and then create a voluntary motor command to look away from the target. The task requires a range of cognitive processes including inhibitory control, attention, working memory, and decision-making [152]. Extensive neuroimaging has been done using the Anti-Saccade task, identifying the frontal eye fields (FEF), supplementary eye fields (SEF), ACC, and DLPFC to be involved in the completion of this task [83, 153].

The Paced Auditory Serial Addition Task (PASAT) was originally developed for individuals with TBI [154]. Since then it has been used in many clinical populations including MS, whiplash, chronic fatigue syndrome and depression [154]. The test is a validated measure used to evaluate attention, executive control, working memory, and information processing speed [154]. Although shown to be valid and sensitive to many clinical conditions, the PASAT is very difficult and often causes extreme frustration and anxiety in participants [155]. The Paced Visual Serial Addition Task (PVSAT) was developed as an alternative to the PASAT and is moderately correlated at all difficulty levels [155]. Clear differences exist between the two in terms of difficulty, with the PVSAT being significantly easier and correspondingly a possible ceiling effect has been reported. One benefit of the visual version is that it solves the input-output interference problem with the PASAT [155]. The cortical regions involved in the PVSAT are mainly in the frontal and parietal lobes (superior and inferior parietal lobe bilaterally, superior frontal gyrus bilaterally, left medial frontal gyrus, left inferior frontal gyrus, and adjacent part of the insula, anterior part of the cingulate gyrus and some cerebellar areas [156].

4.3 EEG Data Collection

Electroencephalographic data was recorded using a 32 channels EEG ASAlab system with Waveguard Technology cap (Advanced Neuro Technology, Enschede, Netherlands). This system is supplied with shielded wires to make recordings less susceptible to external noise and movements. EEG data was continuously recorded using a 500 Hz sampling frequency. The ground electrode (AFz) and common average reference was positioned between Fpz and Fz to ensure low impedance values (generally < 5 KΩ). The 32 electrodes were distributed along the scalp according to the 10/5 system [157]. The cap was fixed with a chinstrap to prevent shifting during the exercise trials and was permeable to air in order to prevent an increase in heat during exercise. Each electrode was filled with OneStep EEG-Gel (H + H Medizinprodukte GbR, Münster, Germany) for improved signal transduction. To ensure consistent cap placement, the vertex (Cz) electrode was placed midway between ears, and midway between the nasion and inion. On the first day, the participants were asked to sit still with their eyes closed for 5 minutes to collect resting state data.

4.4 EEG Data Analysis

Analysis of the EEG signal was completed offline after each participant completed all of his or her visits. The EEG data was exported from the collection device and brought into Brain Electrical Source Analysis® Research (BESA) for analysis. The EEG signals were first filtered using a band-pass filter (4 – 50 Hz) and notch filter (60 Hz) to remove signal drift, line noise and motion artifacts. Independent Component Analysis (ICA) was used to decompose the signal and identify eye blinks, which were then removed from analysis, as were channels with excessive noise. An automated artifact scan was performed to check signal for noise. Participant data was included in analysis as long as 70% of trials were clean of artifacts. The task sent triggers to the

EEG system allowing for the identification of each stimuli presentation. Using the accuracy data, all trials in which the participant responded incorrectly, were removed from further analysis. The data from all accurate trials for each task and block were then averaged using 1.24 seconds epoch (-0.24 – 1000 ms). A 10-10 average virtual montage was applied to the data, resulting in 27 channels. This data was then exported into MATLAB (Version R2013b, The Mathworks, Inc., Natick, MA, USA)). Within MATLAB, using scripts developed in the lab, the average signal from each participant was averaged together to form a single "Grand Average" signal that represented the group's ERP in response to the task. The data was plotted (Figure 5 – 3) to allow for visualization of the ERP over the entire scalp. Using this plot, the signal was visually evaluated and regions that showed significant peaks of activation were highlighted. The brain regions of interest for this study were chosen *a priori* and this process was used to confirm that the chosen regions were in fact involved in the tasks. The visual inspection of the data confirmed our chosen areas of interest with the left, central, and right frontal regions and occipital midline undergoing further analysis.

4.4.1 Power Spectrum Analysis

In BESA, a virtual source montage was applied to the signal. This montage, as discussed in Chapter 2, reconstructs approximate source waveforms that can be used to represent cortical activity. Fast Fourier Transforms (FFT) was then applied to EEG signal, which transforms the data from the time domain to the frequency domain. This allows for the calculation of power at each frequency band. For this study, the data was segmented into theta (4-8 Hz), low alpha (8-10 Hz), high alpha (10-13 Hz), beta (13 - 30 Hz) and gamma (30 – 45 Hz). The output of the FFT was absolute power (nAm^2) and these values were used for statistical analyses.

4.4.2 Brain Connectivity Network Modeling

The data was exported to MATLAB once more under the Virtual Source montage. A local script was used to segment the signal into theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-45 Hz). EEG signal in each frequency band was then run through the connectivity analysis. To compute the brain connectivity networks, the PC controlled false discovery rate (PCFDR) algorithm was used[158]. PCFDR is a computational method based on the error rate criterion of the discovered network. Partial correlation is used to evaluate the conditional independence, which estimates the directed interactions between any two-brain regions after removing the effects of all other brain areas. The PC algorithm starts from a complete graph and tests for conditional independence in an efficient way. The PCFDR algorithm asymptotically controls the false discovery rate (FDR) below the predefined levels, which evaluates the proportion between the connections that are falsely detected to all those detected. Compared to the traditional Type-1 and Type-2 error rates, FDR has more conservative error rate criteria for modeling brain connectivity due to its direct relation to the uncertainty of the networks of interest. The PCFDR algorithm and pseudo-code are described in details in [159]. The FDR threshold was set at the 5% level. The learned connectivity networks are binary undirected graph with the inferred connections at the 5% significance level. The binary undirected networks were computed for each individual for all frequencies, task conditions and blocks independently.

4.4.3 Graph Theoretical Analysis

Graph theoretical analysis was used to extract structural network features from the learned networks [76]. Traditional graph theoretical measures were used to characterize the network features in terms of density, global efficiency, clustering coefficient, and modularity.

The definitions of these measures can be reviewed in Chapter 2. The Brain Connectivity Toolbox [74] was used to perfrom the graph theoretical analysis. For the network, each of the 15 virtual source montage sources represented a brain region within the network.

4.5 Experimental Protocol

This study employed a single group randomized repeated measures design. Interested participants were appropriately screened by a phone interview to ensure they met all of the stated inclusion criteria. Participants deemed eligible were invited to visit the Djavad Mowafaghian Centre for Brain Health (CBH) at the University of British Columbia. Participants were asked to come in to CBH on three (3) different days within a 7-day period, at the same time of day, in order to account for the effect of circadian rhythm on cognition [160]. On the testing days the participants performed one of the three tasks: ASAT, Exercise or ASAT-Exercise dual task. The order of the tasks was randomized to account for any order effect. After initial telephone screening, each participant had his or her task order randomized prior to his or her first visit.

During the first visit to the Centre for Brain Health, each participant was met by the research coordinator and asked to review a written consent form (see Appendix C), as well as encouraged to ask questions as they arose. Physical activity level was quantified using the Recent Physical Activity Questionnaire (RPAQ), which has undergone extensive reliability and validity testing [161]. The RPAQ consists of questions across three (3) different activity domains to determine the individuals' average activity level over the last four (4) weeks (Appendix D). The participant then completed the ASAT task training. This included two decomposed proponents of the task. The total learning period took 30 minutes. Following the task training, the EEG cap was placed on the participants' head, after which they were instructed to sit still for 5 minutes, while keeping their mind clear to allow for the collection of resting state brain activity.

The study procedure was composed of the three testing conditions. The order was randomly assigned immediately following acceptance into the study. After the EEG cap was placed on his or her head, the participants were instructed to sit on the stationary bicycle (Zhejiang Everbright Industry, Inc, Taichung City, Taiwan). Participants were asked to adjust the seat to ensure optimal pedal distance and the bike was then adjusted to keep the wall mounted screen a set distance based off of their height in order to maintain the correct angles for the anti-saccade component of the ASAT. The participants were then instructed to complete one of the three (3) task conditions.

4.5.1 Cognitive Task: ASAT

The task began with a fixation point in the middle of the screen, followed by a distractor stimulus (red dot) being shown for 100 ms at a fixed distance to the left or right of the centre (in random sequence). In the opposite direction to the distractor stimulus, the target stimulus (single digit) was presented for 200 ms (Figure 4 – 1). The task required the participant to mentally track and verbally add the sequentially presented digits. The participants also had to ignore the distractor stimulus, or else they would miss the target stimulus as a result of the time cost attributed to the erroneous pro-saccade. The ASAT was presented using a commercially available stimulus presentation software (E-Prime 2.0, Psychology Software Tools). The task consisted of 5 blocks, with each block increasing in difficulty through changes in the anti-saccade angle, the inter-stimulus interval and number of trials (Table 4 - 1). Participants were instructed to respond verbally as quickly as possible following each stimulus.

Table 4 – 1. Block progressions for the Anti-Saccade Serial Addition Task and Exercise Intensities.

	Block 1	Block 2	Block 3	Block 4	Block 5
ASAT inter-stimulus interval (sec)	3.0	2.5	2.0	1.5	1.0
ASAT distractor off-set (degrees)	5	7.5	10	12.5	15
Heart rate reserve (%)	30	40	50	60	70

4.5.2 Exercise

The participants were asked to change into comfortable clothing for exercise. At this time they were asked to put on a Polar Heart rate monitor band (Polar Electro, Oy, Kempele, Finland). The participant was then asked to sit quietly for 5 minutes in order to measure their resting HR. Using their age, their max HR was calculated using equation 1. Their target HR was then calculated using Equation 2.

$$HR_{Max} = 208 - 0.7 \times Age \tag{1}$$

$$TR_{HR} = (HR_{Max} - HR_{Rest}) \times\% + HR_{Rest} \tag{2}$$

The exercise task was divided into 5 separate blocks of increasing intensity (Table 4 - 1). Based off of the target HR calculated using equation (2) the participant was asked to begin biking at 30% of their heart rate reserve. The research coordinator monitored the participant's heart rate and modulated the intensity of the exercise appropriately by increasing or decreasing the resistance, as the participant was asked to maintain a steady RPM of 60 throughout the task. Once a steady state HR was obtained, the participant continued for 5 minutes. After 5 minutes the participant increased their intensity to 40% and repeated for 50%, 60% and finally 70%. Steady state HR was defined as within +/- 5 beats per minute and was constantly monitored by the research administrator to ensure compliance and adjust the necessary settings.

During the last 30 seconds of each exercise block the participants were shown a Borg intensity scale (Appendix E) and asked to identify their perceived exertion using the scale. Following the final exercise block the participants were instructed to cool down for 5 minutes.

4.5.3 ASAT-Exercise Dual Task

Participants changed into comfortable clothing for exercising and placed the Polar Heart Rate monitor band under their clothing. The participants were asked to sit on the exercise bike while the cap was placed on their head. Once the cap was firmly placed on their head the participants was asked to begin pedaling at 30% of their HRR. Once reaching steady state the ASAT began. At each increase of exercise intensity, a corresponding increase in ASAT difficulty occurred, reaching a max difficulty at the end (Table 1). During the final 30 seconds of each exercise block the participants was shown a Borg intensity scale and asked to identify their perceived exertion on the scale.

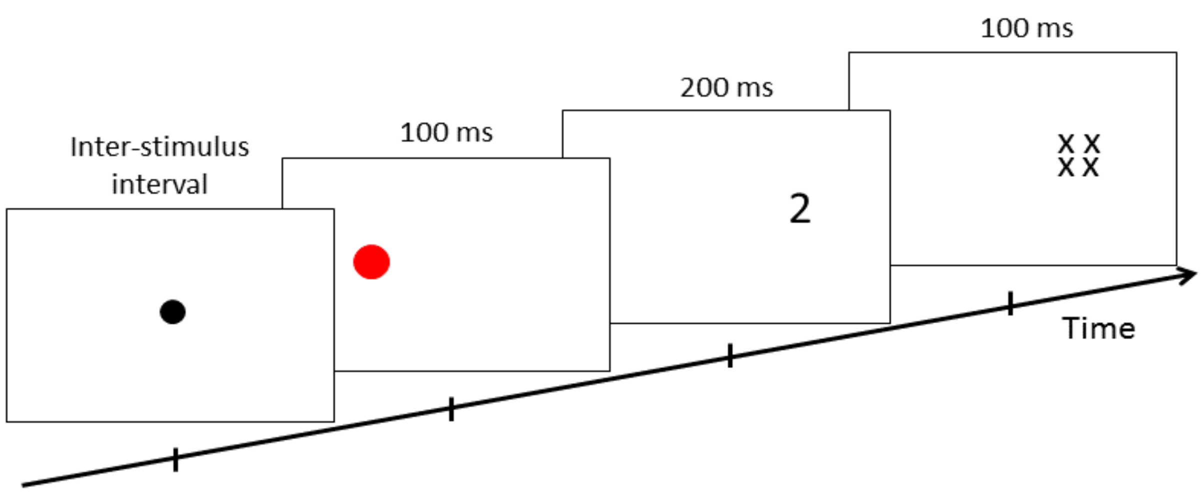

Figure 4 – 1. An example of a single ASAT task trial.

4.6 Outcome Measures

4.6.1 Rated Perceived Exertion

The participants' rated perceived exertion was recorded during each block of the Exercise – only and Combined Cog-Ex tasks using the Borg scale.

4.6.2 ASAT Accuracy

Participant responses were recorded using an electronic recording device. All responses were then input into a database for analysis. The main outcome variable of interest for the ASAT task was response accuracy (%). Accuracy was determined for each block by calculating the correct number of responses and dividing the sum by the total number of trials.

4.6.3 Power Spectrum Analysis

The main outcome variable for the EEG Power spectrum analysis was absolute power, a measure that has been shown to be more responsive to change in exercise studies [134]. Absolute power was compared across tasks (3), loads (5) and brain regions for each frequency.

4.6.4 Functional Connectivity

Based on prior research in our lab, two graph theoretical measures were chosen *a priori* as the main outcome measures for assessing the networks during the various tasks. These critical measures of network connectivity included degree, betweenness centrality, and clustering coefficient.

4.7 Statistical Analysis

4.7.1 Experimental Outcome Measures

The dependent variables for this study included accuracy, absolute power, and the connectivity measures. All statistical tests were performed using IBM SPSS Statistics (Version 23.0.0.0, IBM Corporation, Armonk, New York, USA). A statistician was consulted to ensure appropriate analyses were run to test each of the hypotheses.

A linear mixed model (LMM) was used to model the effect of task condition, levels, regions, and interactions had on the task accuracy and the EEG measures. A LMM was used as it offered more flexibility and a better fit for the data than traditional analyses such as repeated measure ANOVA, ANCOVA, and regression models. Using a mixed model allows for the incorporation of each participant's variability by computing a random slope and a random intercept for each participant, which takes into account the participant differences at each level.

For the behavioural statistical analysis, the model was used to identify differences in task accuracy during the Cognitive-only and Combined Cog-Ex tasks, as well as between difficulty levels. Since the study design had multiple conditions within a single subject, correlation within subject data had to be accounted for.

For the EEG data, the model had Task, Level and Region as fixed effects. Participant and Task type were used as random effects. Task type was considered a random effect as participants performed each task on a separate day. Day to day differences within each of the participants was thereby accounted for within the model.

The model used for most of the analysis was the following:

$$Y = \alpha + \beta_1 Task + \beta_2 Level + \beta_3 Region + a_i + b_i Task + b_i Participant + \in$$

In this model, Y is the dependent variable, either power amplitude or graph theory measure of the EEG signal. α represents the average dependent variable baseline value. $\beta_1 Task,\ \beta_2 Level,$ and $\beta_3 Region$ represent the average task, level, and region effects on the slope of the model. $a_i, b_i Task, and\ b_i Participant$ represent the random variation in the intercept and slope of the model. $\in$ represents the residuals of the model. Residuals from the model were tested for symmetry. A reference for substantial departure from normality was suggested to be an absolute skew of 2 [162]. If the residuals surpassed the skew threshold the data underwent a logarithmic transformation and re-run through the model. Only significant main effects and interactions present in both models are reported. Significance was set at 0.05 and all significant pairwise comparisons were corrected for multiple comparisons through a Bonferroni correction.

Chapter 5: Results

5.1 Participant Characteristics

Due to the extremely limited time available with the EEG cap and system, thirteen (13) participants were recruited to participate in the study. Of this group, eight (8) were males and the remaining five (5) were females. The mean age of the participants was 22.5 years (0.65). The mean years of education was 16.4 years. The average total leisure activity score was 48.0 (5.6) from the Godin Leisure-Time Exercise Questionnaire, indicating the group was very active. [163]. The participants' physical activity level was confirmed by the RPAQ, which revealed a mean of 1.38 hours (0.22) of moderate to vigorous active per day. Table 5-1 provides a summary view of the participant characteristics.

Table 5-1 Participant Characteristics including Age, Gender, Godin Total Leisure Activity score and RPAQ scores.

ID	Age	Gender	Godin Total Leisure Activity Score	RPAQ
P001	22	M	71	3.7
P002	20	F	21	1.4
P003	18	F	64	1.1
P004	21	F	74	1.0
P005	24	M	27	0.9
P006	19	F	34	1.5
P007	25	M	66	1.4
P008	24	M	77	1.5
P009	24	M	44	1.4
P010	23	M	28	1.3
P011	24	F	39	0.9
P012	24	M	50	1.6
P013	25	M	29	0.3
AVERAGE	**22.5**	**M = 8/F=5**	**48.0**	**1.38**
SME	**0.65**		**5.6**	**0.22**

5.2 Behavioural Results

5.2.1 Heart Rate And RPE

Mean Heart Rate and RPE are presented in Figure 5-1 for the Exercise – only and Combined Cog-Ex tasks at each level. Both HR and RPE show no significant effect of task condition, with values being almost identical throughout the levels. The LMM identified a significant effect on Level for both HR and RPE, F (17.9, 107) = 1143.5, p = < .001, F (52.7, 95.05) = 165.88, p = < .001. Post hoc analyses using Bonferroni correction for multiple comparisons revealed significant increase in HR and RPE between each level (p < .001) as both values gradually increased from Block A to Block E.

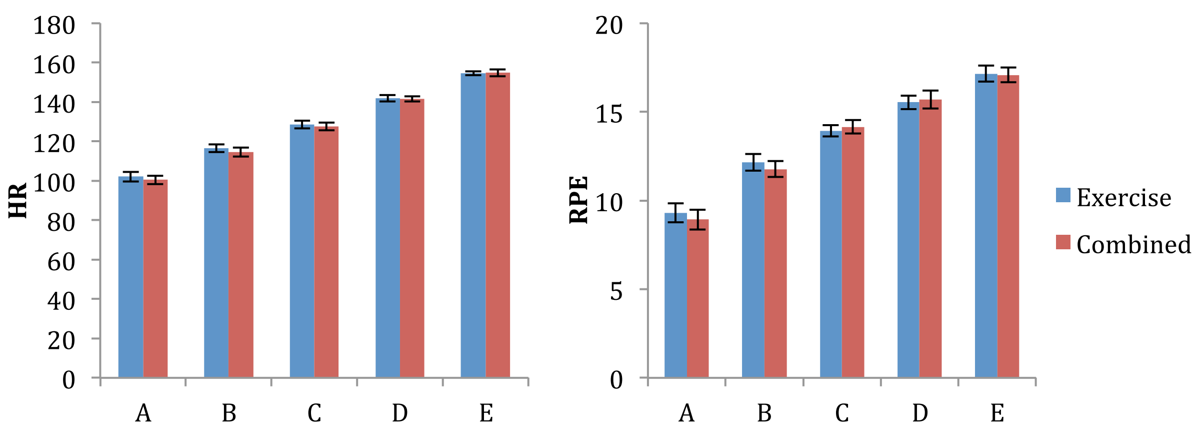

Figure 5 – 1 HR and RPE for the Exercise and Combined Cog-Ex Tasks.
Participant Heart Rate (HR) (Left) showed significant increases between each of the levels in both conditions (p < .001). Rated perceived exertion (RPE) showed a similar pattern, with increased ratings every block (p < .001). Both HR and RPE showed no significant differences between conditions.

5.2.2 Accuracy Of Anti-Saccade Serial Addition Task.

Mean ASAT accuracy was compared between the Cognitive only task and Combined Cog-Ex task, showing that the Combined Cog-Ex task had a lower combined accuracy than the Cognitive-only task although this did not reach significance F (30.5, 55.35) = 3.71, p = .078 (Figure 5 – 2 A). Both task conditions were then combined to assess changes by level of difficulty and are presented in Figure 5 – 2 B. There was a significant main effect for Level, F (30.5, 95.3) = 63.7, p < .001. Post hoc analysis revealed Accuracy was stable during Blocks A – C and showed a significant decrease in the final two blocks.

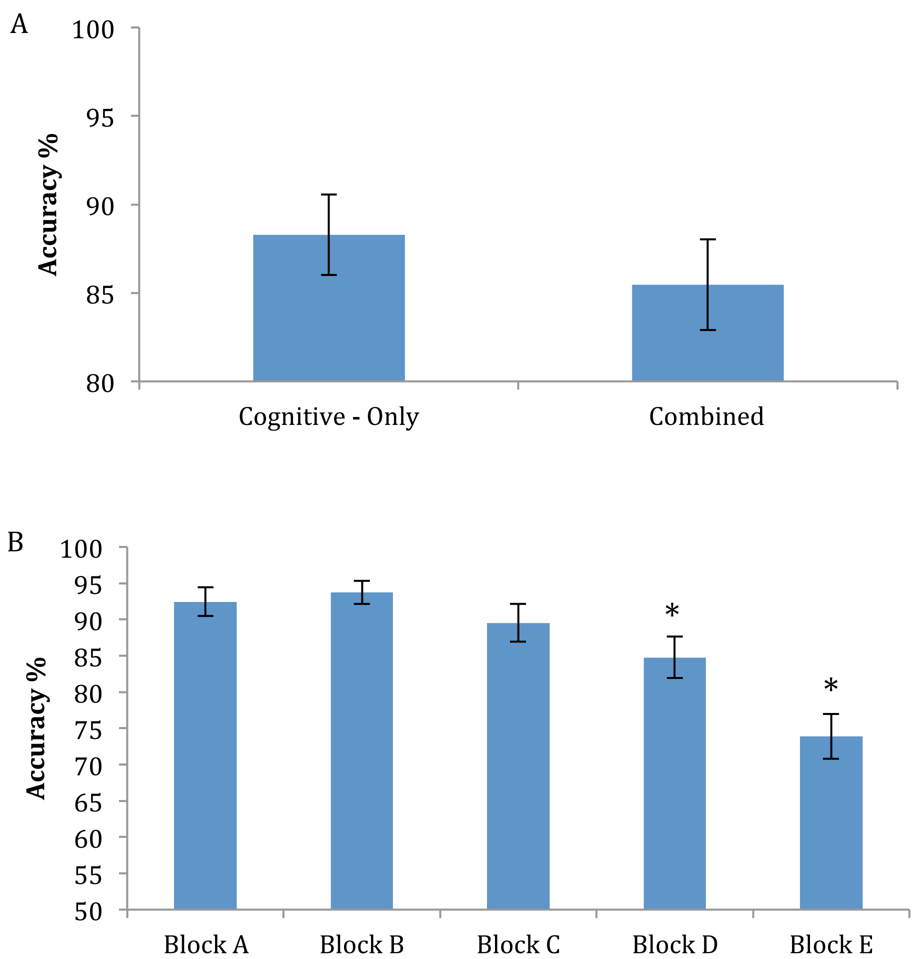

Figure 5 – 2 Working memory task accuracy.

(A) Accuracy differences between task, although not significant ($p = .078$), the Combined Cog-Ex task showed a lower accuracy overall. (B) Combined accuracy (%) of both tasks for each block. There was a significant decrease in accuracy in Blocks D and E ($p < .001$).
* Indicates significance ($p < .05$)

5.3 EEG Results

5.3.1 ERP

The grand averaged ERP was calculated using the 10-10 montage for all blocks for each condition. The frontal regions (F3, Fz, F4) and occipital midline (Oz) were selected *a priori* as regions of interest due to the task design. Figure 5 – 3 illustrates large peaks in activation in these regions during both the Cognitive-only and Combined Cog-Ex tasks, with both tasks showing very similar patterns of activation.

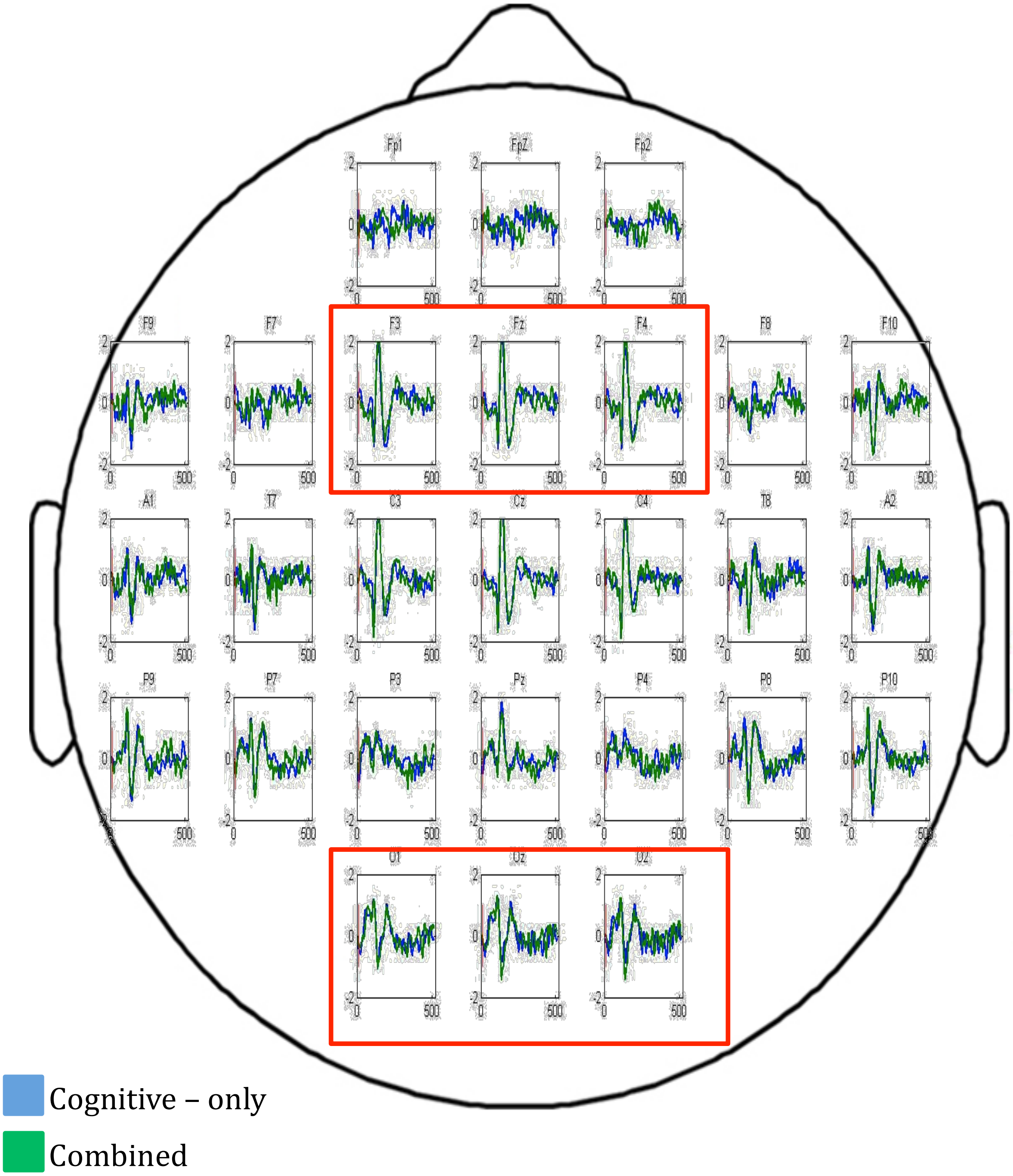

Figure 5 – 3 Visualization of ERP signal over the entire scalp.
Each box represents the ERP signal for that corresponding electrode within the 10-10 montage. Cognitive – only (Blue) and Combined Cog-Ex (Green) show no significant differences in activation pattern. Regions of interest: F3, Fz, F4, O2, Oz, O1 show the expected increase in amplitude during the tasks.

The ERP data was used to confirm the regions of interest and their activation during the various tasks. As a result, the data was evaluated strictly qualitatively and no statistical analyses were performed, as the ERP were not the variables of interest in this study. Figure 5 – 4 shows the changes in the grand average ERP at each block for the regions of interest. Compared to rest, there is an increase in peak amplitude during the first found blocks of the tasks, with all frontal electrodes showing a similar pattern of activation. The occipital region showed a different pattern with less of a significant peak and a more continuous pattern of activation throughout the trial.

Within the frontal electrodes there is a change in pattern of the EEG response during the final block, moving from a large singular peak of activation to a pattern with decreased amplitude but more continuous activation throughout the task.

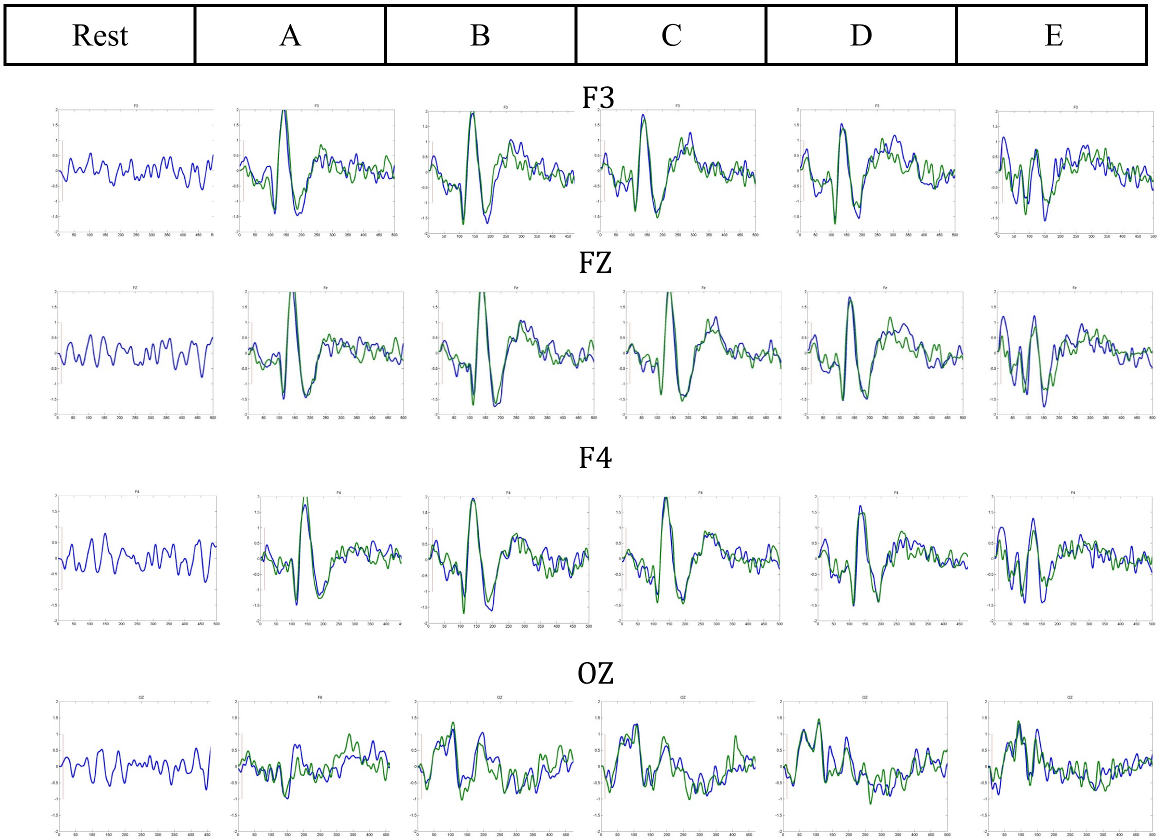

Figure 5 – 4 Group Average ERP during rest and all difficulty blocks.
A clear ERP is discernable from all task conditions compared to the Resting state. For all of the frontal electrodes (F3, Fz, F4) there is little change in activation throughout the first 4 blocks (A-D) before a substantially different signal in Block E. The ERP in Oz is different from the frontal electrodes and shows a signal with increased latency throughout the blocks.

5.3.2 Power Spectrum Analysis

The power spectrum analysis separated the EEG signal into five (5) different frequencies: Theta, low Alpha, high Alpha, Beta and Gamma. Each frequency was run separately through the LMM and will be presented by main effect followed by interactions.

Main Effect: Condition

Figure 5 – 5 shows a significant Main Effect for Condition was found for Theta, $F\,(268.2, 359.7) = 10.68$, $p = .001$. Post hoc analysis revealed Theta power was significantly higher during the

Exercise – only (p < .001) and Combined Cog-Ex (p = .042) tasks compared to the Cognitive – only task condition.

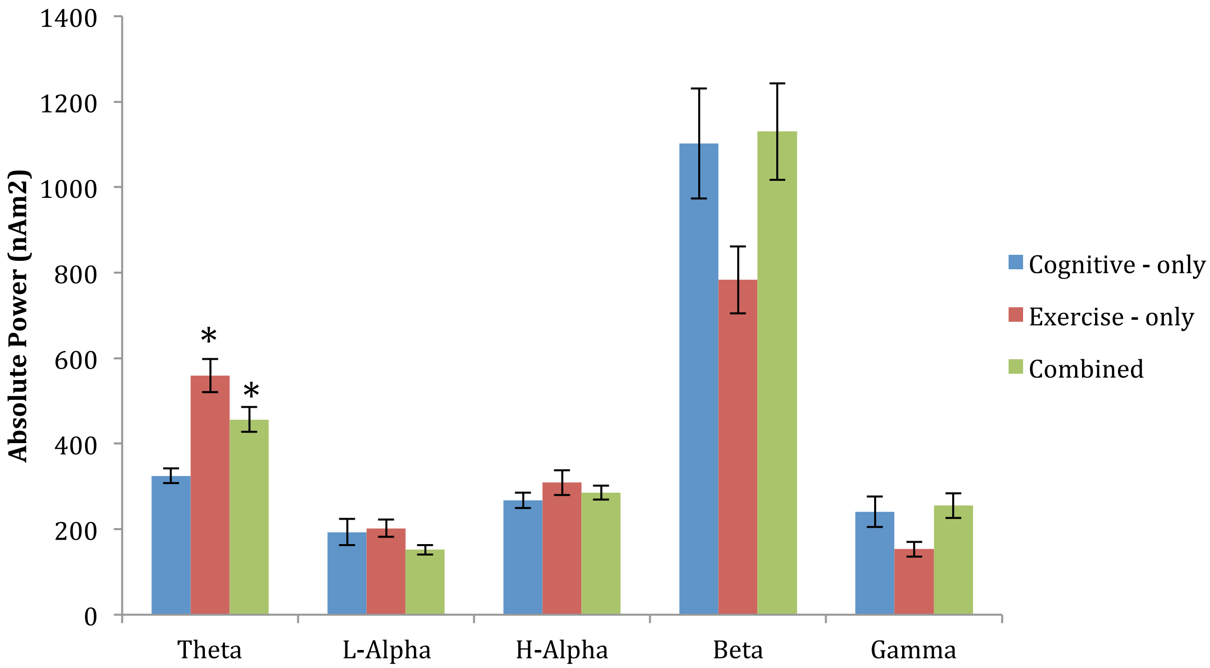

Figure 5 – 5 Absolute Power of the EEG signal for each frequency band.
Minimal fluctuations were seen in most frequency bands. Theta power showed significant differences between conditions, with increased power in both Exercise-only and Combined Cog-Ex tasks over the Cognitive-only condition.
* Indicates significance (p < .05)

Main Effect: Region

A significant main effect of region for theta F (268.2, 665) = 399.55, $p < .001$ was observed (Figure 5 – 6). Post hoc analysis revealed significantly higher power in OpM compared to all frontal regions (p < .001) and lower power in FM (p < .001).

A significant main effect of region for low alpha power F (219.0, 665) = 148.27, $p < .001$ was reported (Figure 5 – 6). Post hoc analysis revealed significantly higher power in OpM compared to all frontal regions (p < .001).

A significant main effect of region for high alpha power F (331.0, 665) = 428.69, $p < .001$ was reported (Figure 5 – 6). Post hoc analysis revealed significantly higher power in OpM compared to all frontal regions ($p < .001$) and lower power in FM compared to all other regions ($p \leq .001$).

A significant main effect of region for beta power (F (226.5, 665) = 214.7, $p < .001$) was reported (Figure 5 – 6). Post hoc analyses revealed significantly higher beta power in OpM and significantly lower in FM compared to other regions ($p < .001$).

A significant main effect of region for gamma power (F (242.4, 665) = 148.6, $p < .001$) was reported (Figure 5 – 6). Post hoc analyses revealed significantly higher gamma power in OpM ($p < .001$) and significantly lower in FM compared to other regions ($p < .05$).

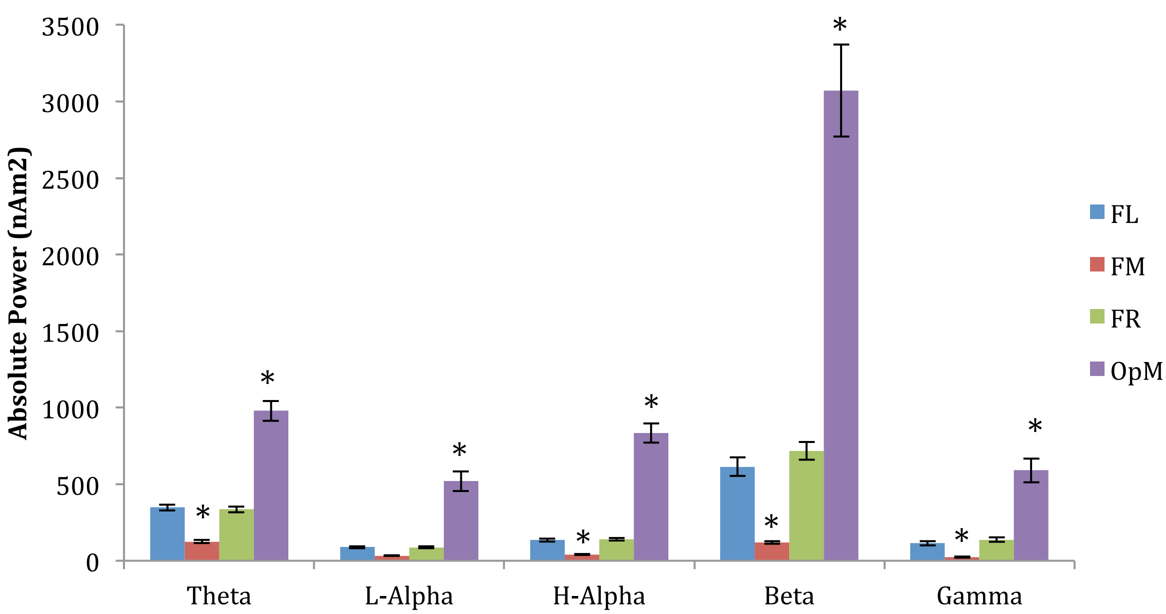

Figure 5 – 6 Absolute Power of the EEG signal from each frequency band by Region. With all tasks combined, power in OpM was significantly higher than any other region for all frequency bands. FM was significantly lower than the other frontal regions and OpM in every frequency except low alpha.
* Indicates significance ($p < .05$)

Main Effect: Level

Figure 5 – 7 shows a significant main effect for level was found for beta, F (226.5, 665) = 4.46, p = .001. Post hoc analysis revealed beta power was significantly higher in Block E ($p < .005$) compared to Blocks B and C when all tasks were considered together.

A significant main effect for level was found for gamma, F (242.4, 665) = 5.87, $p < .001$ (Figure 5 – 7). Post hoc analysis revealed gamma power was significantly higher in Block E ($p < .005$) compared to Blocks A, B and C ($p \leq .001$) and approached significance in Block D ($p = .066$) when all tasks were considered together.

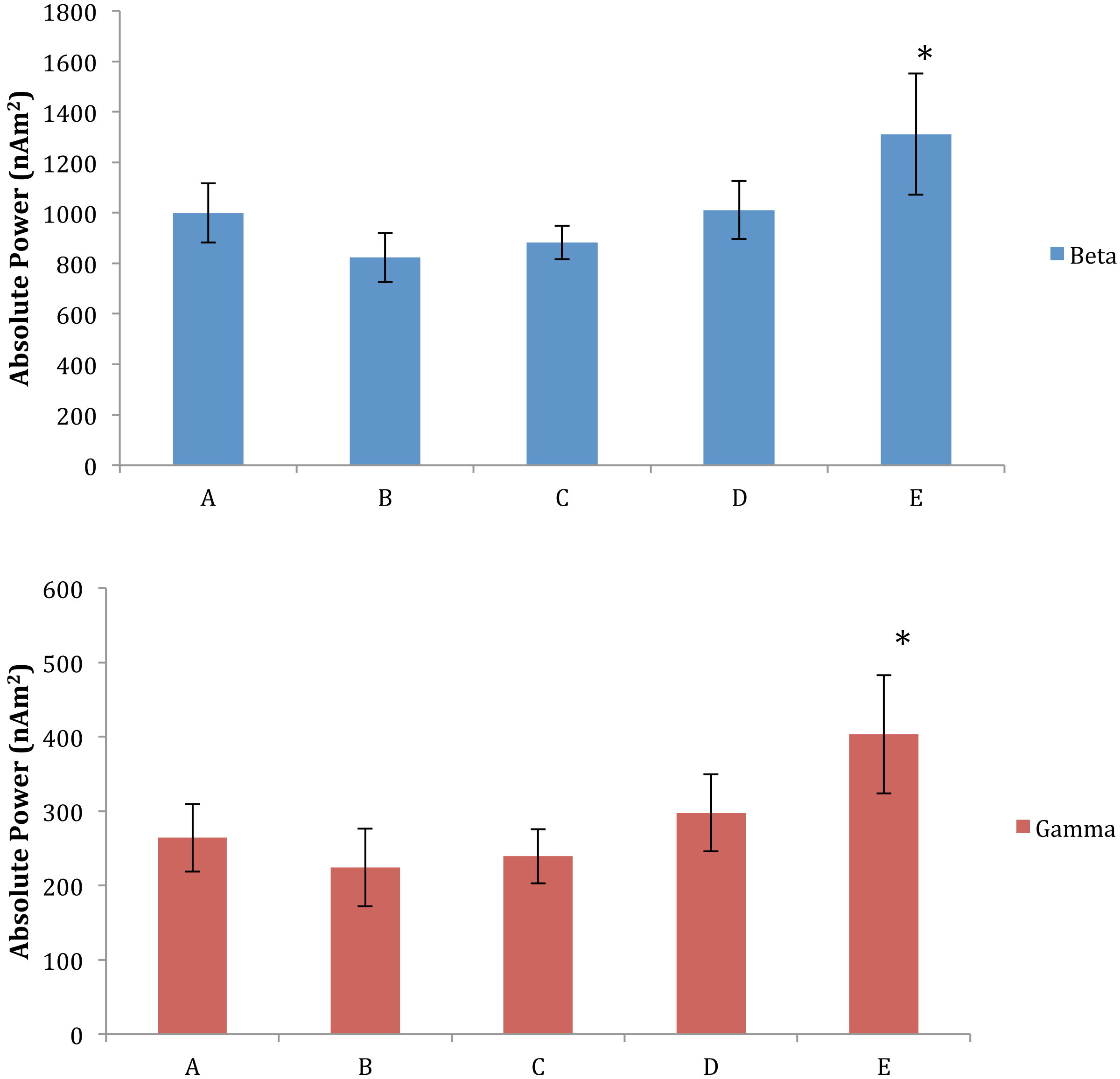

Figure 5 – 7 Absolute Power of EEG signal throughout the blocks.
When tasks and regions are combined, there is a significant increase in Absolute power in the final block (E) in Beta (Blue, top) and Gamma (Red, bottom) frequencies ($p < .005$).
* Indicates significance ($p < .05$)

5.3.3 Functional Connectivity

Global Connectivity

Changes in global functional connectivity were explored using graph theoretical measures and showed no significant changes in density, global efficiency, clustering coefficient, or modularity. The analysis then focused on more localized changes through connectivity between regions.

Local Connectivity

The local connectivity analysis was focused entirely on the frontal brain regions, frontal left (FL), frontal midline (FM) and frontal right (FR), as this was the area primarily expected to be involved in the task.

Main Effect: Task

A significant main effect for task was reported for beta Degree, $F\ (12, 348) = 6.09$, $p = .014$ (Figure 5 – 8). Post hoc analysis revealed a significantly higher value of degree in the Cognitive – only task –keep terms consistent between task and condition compared to the Combined Cog-Ex condition (p = .014).

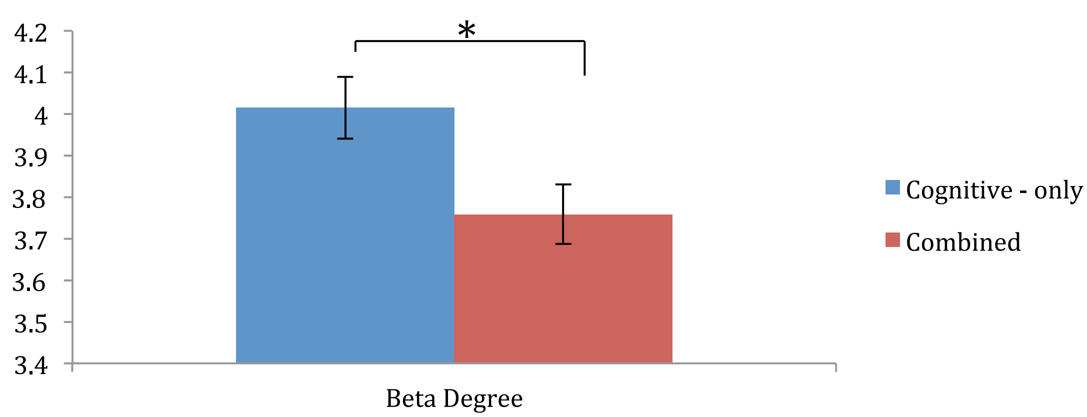

Figure 5 – 8 Changes in graph theoretical measures between the two cognitive tasks.
Beta Degree is significantly lower during the Combined Cog-Ex task than the Cognitive-only task (p < .014).
* Indicates significance (p < .05)

Main Effect: Level

Figure 5 – 9 shows a significant main effect for level with theta Clustering Coefficient, F (12, 336) = 2.59, p = .037. Post hoc analysis revealed Block D to be significantly lower than Blocks B (p = .011) and C (p = .005).

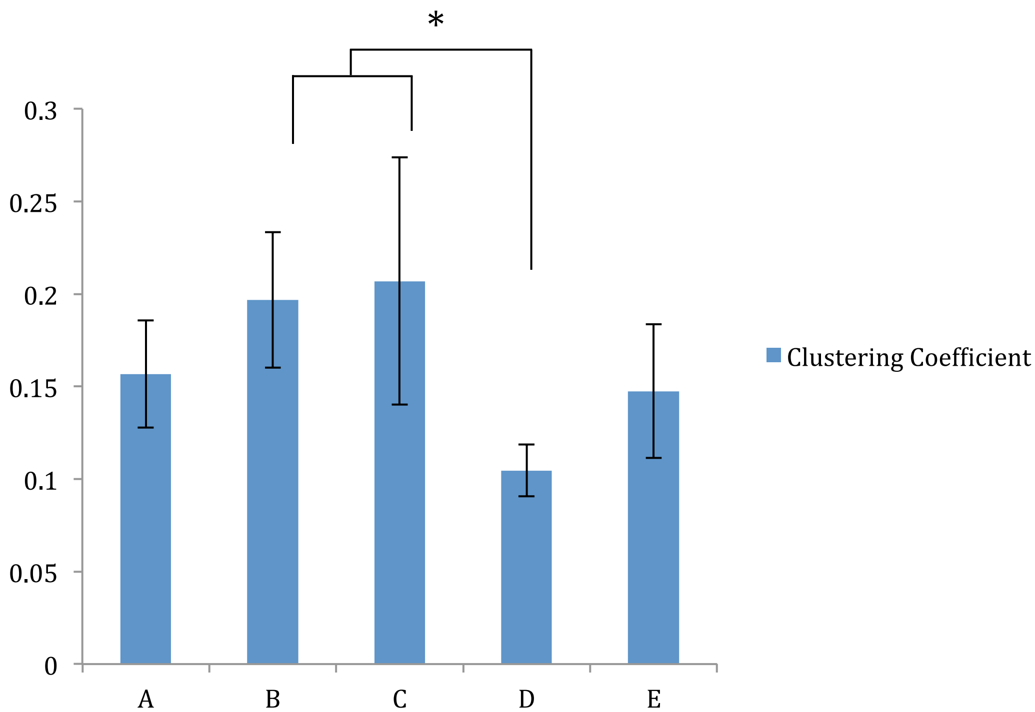

Figure 5 – 9 Changes in Theta Clustering Coefficient through levels.
With both tasks combined, theta clustering coefficient is significantly lower in Block D compared to Blocks B and C.
* Indicates significance (p < .05)

Interaction: Region X Task

A significant Interaction was found for theta Degree, F (12, 348) = 4.18, p = .016 (Figure 5 – 10). Post hoc analysis revealed a significantly higher value of theta Degree in the Cognitive – only task at FM compared to the Combined Cog-Ex condition (p = .029).

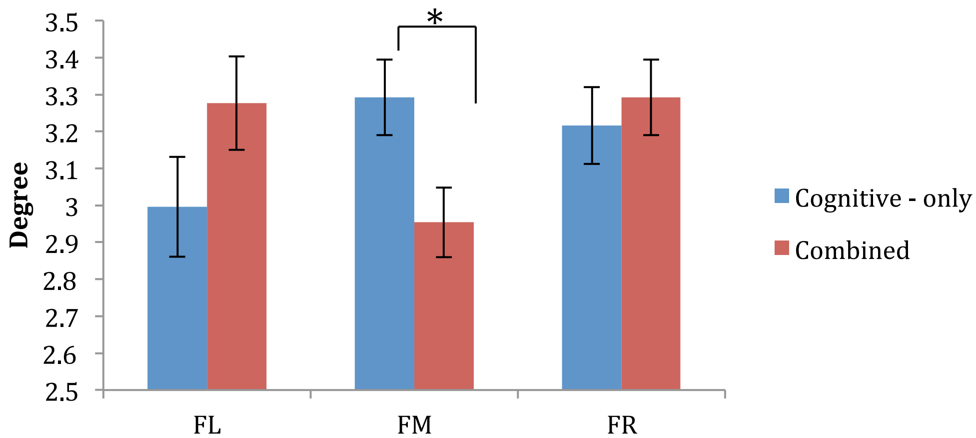

Figure 5 – 10 Theta Degree Region X Task Interactions.
Theta Degree presented with significantly lower values during the Combined Cog-Ex task compared to the Cognitive –only task in FM only (p = .03). The Frontal left and right regions did have the same pattern.
* Indicates significance (p < .05)

There was a significant Region by Task interaction for beta Betweeness, F (360,360) = 3.87, p = .021 (Figure 5 – 11). Post hoc analysis revealed a significantly higher value of beta Betweenness in the Cognitive – only task at FL compared to the Combined Cog-Ex task (p = .007).

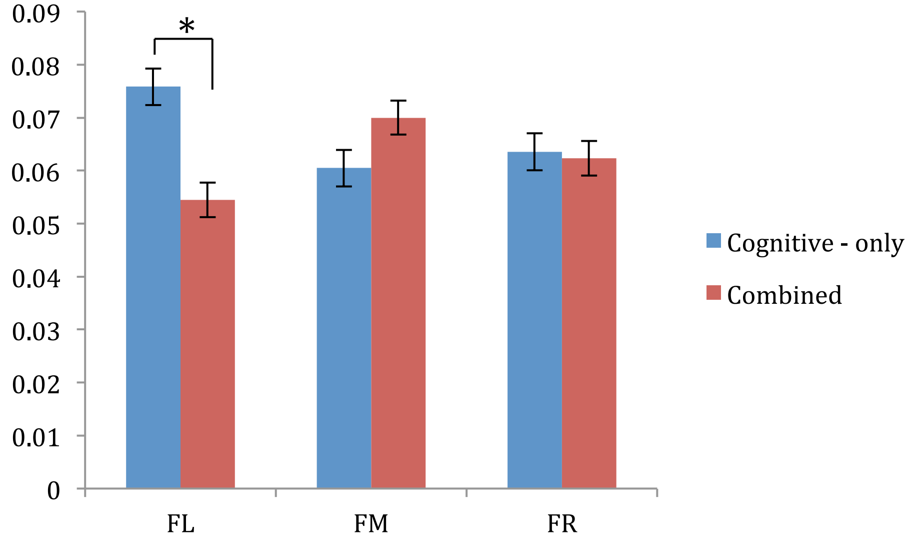

Figure 5 – 11 Beta Betweeness Region X Task Interaction
Beta Betweeness presented with significantly lower values during the Combined Cog-Ex task compared to the Cognitive – only task in FL only ($p = .007$).
* Indicates significance ($p < .05$)

Chapter 6: Discussion

The objective of the current study was to examine the association between EEG metrics and behavioural changes in healthy normal adults as a foundation for evaluating individuals with concussion. In order to accomplish this objective, healthy and physically active participants were asked to complete three tasks: a challenging graded cognitive task, a graded cycling session, and a combined task that had the participants complete both tasks simultaneously. Regarding the exercise paradigm, this study employed a paradigm that forced participants' to place priority on the exercise, by maintaining a speed of 60 rpm throughout the levels and keeping HR within the set level. This forced priority had an influence on the results, as participants were not able to decide themselves on which task to prioritize. This study design was used to reduce the variability in the results and to match the existing literature, which utilized similar paradigms [143, 144, 149, 150]. Our results suggest the graded levels of exercise induced significant changes in both the perceived exertion and heart rate, with both values increasing at each progressive level. This result was seen in both the Exercise-only and Combined Cog-Ex task and suggests that the stepwise progressions were large enough to induce a significant change in the physiological and perceived exertion response.

Between the Cognitive-only and Combined Cog-Ex task there were no statistically significant differences in the accuracy of the task, however there were significant differences in the neural activity. Specifically, theta absolute power was found to be modulated by the task condition. The Combined Cog-Ex task condition elicited significantly greater activity in the frontal brain regions within the theta frequency band compared to the Cognitive-only condition. These results suggest that when exercise is added to the cognitive task, greater attentional resources are required in order to maintain accuracy. Multiple studies have identified theta activity to be positively correlated with cognitive load and accuracy of the task [92, 93, 95]. This result contributes to the current literature regarding theta's active role in cognition.

Consistent with literature using cognitive tasks, as the ASAT increased in difficulty, there was a significant decrease in the accuracy. Specifically, a significant decrease was noted in the final two levels (Blocks D and E), while no significant changes were recorded in the first three blocks. These results suggest that only tasks with a high level of cognitive difficulty result in a decrease in accuracy. The addition of the EEG data allows for the exploration of the impact task type and cognitive load has on neural activity as well as the relationship between the behavioural and neural levels of measurement.

Between the tasks levels there were significant changes in activity within the beta and gamma frequency bands. In particular, a significant increase was found during the final level of the tasks in both frequencies, coinciding with the largest decrease in accuracy. Beta and gamma activity has previously been identified to be involved in many aspects of cognition, including working memory. Beta activity has shown to be sensitive to working memory load, especially during tasks requiring no physical response, as physical movement attenuates activity in this frequency band [103]. Gamma activity meanwhile, is associated with attention and memory formation. Within working memory, gamma has shown to be involved in the maintenance phase of the task and increase almost linearly with load [104, 107]. The reported increased beta and gamma power as the cognitive task increased in difficulty suggests that increased activation was required to complete the task. Furthermore, there was a change in the pattern of activation of the EEG signal within the frontal brain regions during the hardest level of the cognitive task. The signal pattern went from a single, easily identified peak to a more continuous activation throughout the trial. These two results suggest the brain utilizes two strategies to manage the increase in difficulty – increases activity in frequency bands involved with cognition and alters the pattern of activation from a singular peak to a more continuous level of activation. This results in an overall increase in neural activity, which extends over a longer period of time.

During the Combined Cog-Ex task there were changes in connectivity within the frontal brain regions. In particular, beta degree was significantly lower during the combined Cog-Ex task condition compared to the Cognitive-only condition. Degree is a measure of network connectedness and nodal importance to the network. The higher the value of degree of a particular node, the more central and important the node is to the network as a whole. The reported decrease in degree during the Combined Cog-Ex task suggests that with the addition of exercise, the frontal network becomes less central, or important, to the performance of the task. Future studies should explore how the network changes and which regions become more involved during the combined task condition by including a greater number of nodes in a variety of brain regions.

As with the behavioural and earlier neural measures, there was a significant load effect within the functional connectivity measures. Theta clustering coefficient was shown to decrease as the cognitive load increased. Clustering coefficient is an important measure of local connectivity, as it measures the network being composed of small local clusters of connections. Healthy brain networks are characterized as being a small-world network, meaning it has short path lengths and high levels of clustering coefficient. During WM tasks clustering coefficient has been shown to be load dependent, increasing with high cognitive load [113]. The results from this study contrast with this consensus as clustering coefficient was found to decrease with increasing difficulty. A possible explanation for this contrasting result is the fact that both the Cognitive – only and Combined Cog-Ex task conditions were assessed together. Due to the small sample size, it was not feasible to assess the conditions individually. It is possible that the current results suggest that as the task increases in difficulty, the frontal brain regions shift from an efficient and densely connected network to a larger, less efficient and less exclusive network involving other nodes outside of the frontal brain regions. Another possible explanation is that when the added exercise component reaches a certain level of difficulty, the neural activity shifts to accommodate the exercise, thereby altering the network away from a frontally centered network. Future studies should explore this possibility by increasing the sample size and assessing the two conditions individually.

6.1 Limitations

Several limitations are present in this pilot study exploring the association between EEG metrics and behavioural changes in healthy normal adults during various sources of load. As note previously, the statistical power was limited in this study due to a small sample size, further research should be done using a larger sample as well as a group with concussion history. Although significant differences were noted between tasks, a larger group would be beneficial in assessing the differences between levels as well as the Task X Level interactions.

This study utilized a novel task that has not been compared directly to similar tasks. A study incorporating this new task along with the PASAT or PVSAT could be beneficial and allow for an improved comparison between the scores as we noted large differences in accuracy scores between the ASAT and the PASAT/PVSAT in similar populations. Future studies should include both tasks to elucidate how comparable the tasks truly are.

A final limitation of this study was the small number of nodes used in the analysis. This greatly limited the ability to assess the cortical changes caused by the various sources of load.

Future studies should include areas outside the PFC to get a better understanding of the impact on the whole brain. The functional connectivity analysis was particularly limited in this study as we were unable to identify how the connectivity was influenced by the exercise.

6.2 Applications For Sports Related Concussion

This study provides the framework for future studies to investigate the differences in neural activation between healthy individuals and those recently recovered from sports-related concussion. The results imply that the addition of exercise has a measurable impact on neural activity and individuals recovering from SRCs would require greater neural resources that may not be available following injury. This would result in a measurable decrease in accuracy during a cognitive and exercise combined task condition. This information could be used in addition to symptom reporting to aid in identifying when athletes are able to return to play safely. To the author’s knowledge this is the first study to explore brain activation using power spectrum analysis and graph theoretical analysis during a combination of exercise and cognitive function and the relationship with behavioural scores. Future research should consider larger sample sizes in addition to including both healthy and concussed groups.

Chapter 7: Conclusion

This study explored the cortical activity associated with the completion of a novel working memory cognitive task, an exercise task and a combined task in healthy young adults. Our results indicate that combining graded exercise and cognition results in significant changes in both behaviour and cortical activity. When compared to either the Exercise - only or Cognitive – only task condition, the Combined Cog-Ex condition results in significant overall changes in brain and behaviour that is observable in EEG signal pattern, EEG power output, and in local functional connectivity metrics within the frontal regions of the brain. These results provide new information regarding the impact exercise has on neural activity and could have applications in future studies involved in concussion recovery.

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Appendices

Appendix A: Godin Leisure-Time Exercise Questionnaire

<u>**Godin Leisure-Time Exercise Questionnaire**</u>

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week	Duration (minutes)
a) **STRENUOUS EXERCISE (HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	________	________
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	________	________
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	________	________

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	RARELY
☐	☐	☐

Days Per Week: ____________

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Appendix B: Study Recruitment Flyer

Research Study

Investigating How the Brain is Influenced by Exercise and Cognition

We are inviting HEALTHY adults between the ages of 18-25 to participate in a research study to measure how the brain reacts to exercise and cognition seperatley and combined. This research will be conducted at the Perception-Action lab at the University of British Columbia under the supervision of Dr. Virji-Babul. If you are eligible and decide to participate, you will be invited to complete 3 sessions (within 7 days), each lasting 1 hour, which will involve wearing a NEW EEG head cap while peforming the tasks.

If you are interested, please contact:
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Brain Activation Study
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Appendix C: Study Consent Form

a place of mind
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Characterization of Prefrontal Cortex Activation in Young Adults During a Stepwise Cognitive and Physical Loading Dual Task: an EEG Study
Informed Consent

Principal Investigator: Naznin Virji-Babul, PT, PhD. Dept. of Physical Therapy, Faculty of Medicine (604-827-4966)

Study Team Members: Shaun Porter, Bsc. (UBC)

Invitation to Participate:
You are being invited to participate in this research study to help with the characterization of the changes in brain activation during a cognitive task, an exercise session and a dual task that combines the cognitive task and exercise. The purpose of this study is to further our understanding of the healthy brain and quantify any changes in brain activation as a result of the exercise. Findings from this study will allow future research to look at other groups of people such as those recovering from concussion.

Participation is Voluntary:
Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reason for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

Purpose

The purpose of this study is to characterize normal brain activation in young adults during challenging mental and physical tasks. This will be done using electroencephalography (EEG) under various conditions. The results from this study will help advance the knowledge on how the brain is activated during exercise and during cognitive tasks. This study will also provide knowledge on the feasibility of using an EEG system to image brain activation under various situations.

Who Can Participate in this Study?

You have been identified because you are between the ages of 18-25, regularly participate in physical activity and have no previous history of concussion or other neurological conditions. If you agree to take part in the study, Dr. Virji-Babul or her associates will determine if you have any condition that will prevent you from being in the study. Screening should take no more than 5 minutes.

Who Should Not Participate in this Study?

You should not participate in this study if you have a history of seizure, epilepsy, neurodegenerative disorder, major head trauma, or a psychiatric diagnosis. You should not participate in this study if you have severe vision or hearing impairment.

What Does the Study Involve?

If you are eligible and decide to participate in this study, you will come to the Perception-Action Lab (3450 Mowafaghian Centre for Brain Health, UBC) for three (3) visits, each expected to last a maximum of 1 hour.

1. Training and Resting State

   One of the research staff will meet you at the main doors of the Mowafaghian Centre for Brain Health to bring you to the Perception-Action Lab. An electroencephalogram (EEG) is a technique for studying the electrical current within the brain. Electrodes are attached to the scalp. Wires attach these electrodes to a machine, which records the electrical impulses. The results are either printed out or displayed on a computer screen. You will not be able to use hair products before coming in for your appointment; this includes conditioner, mousse, hairspray, etc. Shampoo is fine. You will then be asked to sit in a chair. On the first visit you will be asked to complete a Recent Physical Activity Questionnaire (RPAQ) which gathers information regarding your average physical activity level in the last month. Following this, you will be asked to complete a training period of the cognitive task. This will take approximately 30 minutes. Upon completion you will then be asked to put on the Polar Heart Rate Monitor and bike on the stationary bicycle for 5 minutes to get comfortable with the model. The EEG head cap will then be placed over your forehead and secured. You will then be asked to sit quietly for 5 minutes with your eyes closed.
2. Single and Dual Tasks

   You will be asked to come to the Centre for Brain Health on three (3) separate occasions, within 7 days. Each day you will complete one of the following tasks, with the order randomized:

1. Anti-saccade Serial Addition Task (ASAT)
    a. On this day you will be asked to sit on the recumbent exercise bike and will have the EEG headcap placed over your forehead. You will then be asked to sit still and complete the task. The ASAT is a visual task requiring you to add the second number to the first and the third to the second and so on. There will also be a red dot flash on the screen. You are not to look at the dot or else you will miss the upcoming number. The task is broken down into 5 blocks, each block increasing in difficulty. The task should take approximately 20 minutes to complete. Following completion the cap will be removed.
2. Exercise exertion Task
    a. On this day you will be asked to put on the Polar Heart Rate Monitor and sit on the recumbent bicycle. The EEG cap will then be placed on your forehead. You will then be asked to pedal at your own pace for 5 minutes to warm up. The exercise task will then begin. The task is divided into 5 blocks of increasing intensity, going from 30% to 70% of your Heart Rate max. At the end of each block you will be asked to rate your perceived exertion level on a scale from 1 – 10. Following the final block the session will be complete and you will complete a cool down.
3. Dual Task
    a. On this day you will be asked to put on the Polar Heart Rate monitor and sit on the recumbent bicycle. The EEG cap will then be placed on your forehead. You will then be asked to pedal at your own pace for 5 minutes to warm up. Following this the dual task will begin. Once again the task is divided into 5 blocks with both the exercise intensity and ASAT difficulty increasing simultaneously. At the end of each block you will be asked to rate your perceived exertion level on a scale from 1 – 10. Following the final block the session will be complete and you will complete a cool down.

Once all three days of testing is complete, your participation is complete.

What Are Possible Harms and Side-Effects of Participation?
The risks are not greater than the risks in everyday life. These procedures will be conducted according to published safety standards. Dr. Virji-Babul or her associates have discussed this research with you and have described them as follows:

Electroencephalography (EEG): Collection of EEG involves the placement of surface electrodes on your skin. This allows for the detection of electrical brain signals. You will feel little or no discomfort during the EEG. The EEG only records electrical brain activity and will not transmit any sensations.

You will be asked to complete two (2) exercise sessions lasting roughly 20 minutes each on a stationary bicycle. You will be wearing a heart rate monitor and asked to keep your heart rate within a set range. You may experience some discomfort. If at any point during the exercise sessions you feel the need to stop, the session will be stopped immediately.

There may be other risks that have not yet been identified, and unexpected side effects that have not been previously observed may occur.

What are the Benefits to You of Participating in the Study?
There is no direct benefit to you for participating in this study. It is hoped that information gained in this research study may be useful in understanding the impact of exercise on brain function.

Payments to Subjects
You will receive three (3), $10 Starbucks Gift cards, one at the end of each day of participation to thank you for coming to UBC and participating in the study.

Confidentiality:
Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

If the results of this study are published or presented in public, information that identifies you will be removed. If you decide not to sign the form, you cannot be in the study.

Your participation in this study is voluntary and you may withdraw at any time. You do not need to provide a reason for your withdrawal. The data we collect up to the point of your withdrawal from the study will be kept for data analysis purposes under strict provisions of confidentiality.

By signing this form, <u>you do not give up any of your legal rights</u> and you do not release the study investigator or other participating institutions from their legal and professional duties. There will be no costs to you for participation in this study. You will not be charged for any research procedures.

Questions
You have read the information in this form. Dr. Virji-Babul or her associates have answered your question(s) to your satisfaction. You know if you have any more questions after signing this you may contact Dr. Virji-Babul or one of her associates at 604-827-4966 or 604-827-2717.

Contact for information about the study:
If you have any questions or desire further information with respect to this study, you may contact Dr. Naznin Virji-Babul at 604-827-4966.

Contact for concerns about the rights of research subjects:
If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the UBC Office of Research Ethics at 604-822-8598 or if long distance e-mail RSIL@ors.ubc.ca or call toll free 1-877-822-8598.

Consent to Participate

Characterization of Prefrontal Cortex Activation in Young Adults During a Stepwise Cognitive and Physical Loading Dual Task: an EEG Study

- I have read and understood the subject information and consent form.
- I have been told that I will receive a dated and signed copy of this form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the chance to ask questions and have received satisfactory answers.
- I understand that all of the information collected will be kept confidential, and that the results will only be used for scientific objectives.
- I understand that my participation in this pilot study is voluntary and that I am completely free to refuse to participate or to withdraw from this pilot study at any time.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that that this pilot study will not provide any direct benefit to me.
- I have read this form and I freely consent to take part in this pilot study.

Participant's Signature	Participant's Printed Name	Date

Signature of Person Obtaining Consent	Printed Name, Study Role	Date

Investigator Signature	Printed Name	Date

My signature above signifies that the pilot study has been reviewed with the participant by me and/or by my delegated staff. My signature may have been added at a later date, as I may not have been present at the time the participant's signature was obtained.

Appendix D: Recent Physical Activity Questionnaire (RPAQ)

Djavad Mowafaghian
CENTRE FOR BRAIN HEALTH

Participant study No.

NSERC
CRSNG

RPAQ

Recent Physical Activity Questionnaire

This questionnaire is designed to find out about your physical activity in your everyday life in the last 4 weeks

This questionnaire is divided into 3 sections
Please try to answer every question.

- **Section A** asks about your physical activity patterns in and around the house.
- **Section B** is about travel to work and your activity at work.
- **Section C** asks about recreations that you may have engaged in during the last 4 weeks.

Your answers will be treated as strictly confidential and will be used only for medical research

Section A Home Activities

Getting about

Which form of transport have you used **most often** in the last 4 weeks apart from your journey to and from work? (Please tick (9) one box only)

Usual mode of travel			
Car / motor vehicle	Walk	Public transport	Cycle

TV, DVD or Video Viewing (Please put a tick (9) on every line)

Hours of TV, DVD or video watched per day	Average over the last 4 weeks					
	None	Less than 1 hour a day	1 to 2 hours a day	2 to 3 hours a day	3 to 4 hours a day	More than 4 hours a day
On a weekday before 6 pm						
On a weekday after 6 pm						
On a weekend day before 6 pm						
On a weekend day after 6 pm						

Computer use at home *but not at work* (e.g. internet, email, Playstation, Xbox, Gameboy etc) (Please put a tick (9) on every line)

Hours of home computer use per day	Average over the last 4 weeks					
	None	Less than 1 hour a day	1 to 2 hours a day	2 to 3 hours a day	3 to 4 hours a day	More than 4 hours a day
On a weekday before 6 pm						
On a weekday after 6 pm						
On a weekend day before 6 pm						
On a weekend day after 6 pm						

Stair climbing at home (please put a tick (9) on every line)

Number of times you climbed up a flight of stairs (approx 10 steps) each day at home	Average over the last 4 weeks					
	None	1 to 5 times a day	6 to 10 times a day	11 to 15 times a day	16 to 20 times a day	More than 20 times a day
On a weekday						
On a weekend day						

Please answer this section to describe if you have been in paid employment at any time **during the last 4 weeks** or you have done regular, organised voluntary work.

Have you been in employment during the last 4 weeks? *Yes* ☐ *No* ☐

During the last 4 weeks how many hours work did you do per week?

	4 weeks ago	3 weeks ago	2 weeks ago	1 week ago
Work hours (excluding travel)				

Type of work

We would like to know the type and amount of physical activity involved in your work. **Please tick** (9) the option that **best** corresponds with your occupation(s) in the last 4 weeks from the following four possibilities:

Please tick only one of the following

1. Sedentary occupation
You spend most of your time sitting (such as in an office) ☐

2. Standing occupation
You spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard) ☐

3. Manual work
This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter) ☐

4. Heavy manual work
This implies very vigorous physical activity including handling of very heavy objects (e.g. dock worker, miner, bricklayer, construction worker) ☐

Section B Activity at work

Travel to and from work in the last 4 weeks

What is the approximate distance from your home to your work?

☐☐☐ Miles *or* ☐☐☐ Kilometers

How many times a week did you travel from home to your main work? ☐☐

Count outward journeys only

Please tick (9) one box **only** per line

How did you normally travel to work?	Always	Usually	Occasionally	Never or rarely
By car/motor vehicle				
By works or public transport				
By bicycle				
Walking				

What is the postcode for your main place of work during the last 4 weeks?

Postcode ☐☐☐☐ ☐☐☐

If not known please give your work address

Work address - ________________________________

____

____

What is the postcode for your home address?

Postcode ☐☐☐☐ ☐☐☐

Section C Recreation

The following questions ask about how you spent your leisure time.

Please indicate how often you did each activity on average over the last 4 weeks

Please indicate the average length of time that you spent doing the activity on each occasion.

Example

If you went walking for pleasure for 40 minutes once a week.
If you had done weeding or pruning every fortnight and took 1 hour and 10 minutes on each occasion.
You would complete the table below as follows:

Please give an answer for the NUMBER OF TIMES you did the following activities in the past 4 weeks and the AVERAGE TIME you spent on each activity.

Please complete EACH line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Weeding and pruning			9					1	10
Walking for pleasure				9					40

Now complete the table on pages 6 and 7

Please give an answer for the average time you spent on each activity and the number of times you did that activity in the past 4 weeks

Please complete each line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Swimming - competitive									
Swimming leisurely									
Backpacking or mountain climbing									
Walking for pleasure *(not as a means of transport)*									
Racing or rough terrain cycling									
Cycling for pleasure *(not as a means of transport)*									
Mowing the lawn									
Watering the lawn or garden									
Digging, shovelling or chopping wood									
Weeding or pruning									
DIY e.g. carpentry, home or car maintenance									
High impact aerobics or step aerobics									
Other types of aerobics									
Exercise with weights									
Conditioning exercises e.g. using a bike or rowing machine									

Please complete each line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Floor exercises e.g. stretching, bending, keep fit or yoga									
Dancing e.g. ballroom or disco									
Competitive running									
Jogging									
Bowling- indoor, lawn or 10 pin									
Tennis or badminton									
Squash									
Table tennis									
Golf									
Football, rugby or hockey									
Cricket									
Rowing									
Netball, volleyball or basketball									
Fishing									
Horse-riding									
Snooker, billiards or darts									
Musical instrument playing or singing									
Ice skating									
Sailing, wind-surfing or boating									
Martial arts, boxing or wrestling									

Thank you.

Appendix E: Borg Scale

Rating	Description
6	NO EXERTION AT ALL
7	
8	EXTREMELY LIGHT
9	
10	VERY LIGHT
11	
12	LIGHT
13	
14	SOMEWHAT HARD
15	
16	HARD (HEAVY)
17	
18	VERY HARD
19	EXTREMELY HARD
20	MAXIMAL EXERTION