The Effect of Aerobic Exercise on Executive Function and Brain Activity in Traumatic Brain Injury

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Table of Contents

List of Tables

TABLES FROM CHAPTER III

TABLES FROM CHAPTER IV

List of Figures

FIGURES FROM CHAPTER I

FIGURES FROM CHAPTER II

FIGURES FROM CHAPTER III

FIGURES FROM CHAPTER IV

CHAPTER I.

INTRODUCTION

Background of Traumatic Brain Injury

Trauma to the brain can change the essence of a person as well as the planned course of their life. Individuals with traumatic brain injury (TBI) often feel isolated. But in reality, they join the ranks of one of the most common neurological diagnoses in the United States after CVA.[1] During the past 30 years, there have been vast improvements in the development of medicine, neuroscience, and epidemiology that have led to the survival, rehabilitation, and understanding of persons surviving TBI. In a recent position statement supported by the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, the National Institute of Neurological Disorders and Stroke, the Department of Veteran's Affairs, and the National Institute on Disability and Rehabilitation Research in 2010, "TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force." [2] Alteration in brain function is defined as having one of the following signs:

- Any period of loss or decreased consciousness (LOC) or alteration in mental state at the time of injury.
- Any loss of memory of events immediately before or following the injury (PTA).
- Neurologic deficits (loss of balance, dizziness, change in vision, paresis/plegia, sensory loss, language or cognitive deficits, etc).

Other evidence of brain pathology includes evidence from visual neuroradiologic, or laboratory confirmation of brain damage and may include:

- The head being struck by an object.
- The head striking an object.
- The brain undergoing acceleration/deceleration movement without direct external trauma to the head.
- A foreign object penetrating the brain.
- Forces generated from a blast or explosion.

It is estimated by the U.S. Department of Health and Human Services Centers for Disease Control (CDC) that an estimated 1.7 million people sustain a TBI annually.[3] Of those, approximately 52thousand die and 1.6 million will receive some medical care. Falls were the leading cause of TBI (35.2%) and were highest for children and older adults. This was followed by motor vehicle/traffic accidents (MVA) (17.3%), being struck by/against (16.5%), assault (10%), and unknown circumstances 21%.[3]

It is also important to note that the data from the CDC does not include TBI that has occurred in relation to military service. TBI reported in the U.S. armed forces between the years 2000-2011 include an additional 220,430 people making TBI one of the most common neurological diagnoses in the United States.[1,3] Statistically, both active duty and reserve service members are at increased risk for sustaining TBI compared to their civilian peers. This is a result of several factors, including that the military demographics, which is primarily young men between the ages of 18 and 24, which is the age range that is most likely to sustain a TBI. [1, 3] Injuries sustained in the military are due to many causes, including those incurred by their civilian counterparts. However, with

the onset of Operation Iraqi Freedom and Operation Enduring Freedom, the prevalence of TBI has risen dramatically in the U.S. military population due to injuries sustained in blasts exposures from improvised explosive devices (IEDs), suicide bombers, land mines, mortar rounds, and rocket-propelled grenades. The combined result of TBI sustained in both the civilian and military populations result in an estimated $60 billion in both direct medical costs and indirect costs in the U.S. each year. That is a significant cost, in a time where financial resources are limited. [4] It is thereby essential to find meaningful and effective treatments for survivors of TBI which both contain the cost to society and also aid this population to obtain their highest functional ability.

1.1. Pathophysiology of Traumatic Brain Injury

The biomechanics of TBI are often described as focal and/or diffuse. Focal injuries consist of contusions, lacerations, hematomas (epidural or subdural), and tentorial/tonsillar herniation. Focal damage can also occur between the brain and skull as *coup* (at the site of original impact) or *contrecoup* (opposite the side of original impact) (Fig. 1.1).

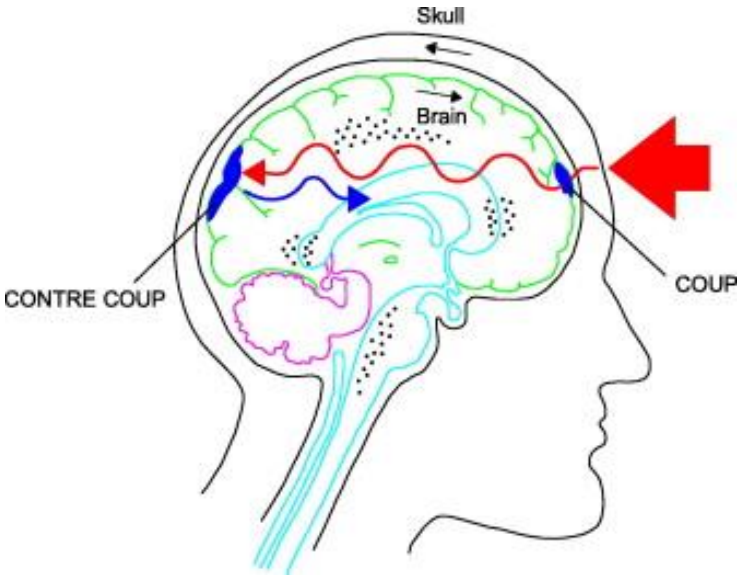

Figure1.1 Coup–contrecoup injury[14]

Coup contusions are produced by the slapping effect of the skull hitting the brain. Contrecoup lesions follow from the bouncing of the brain against the inner posterior surface of the skull with the possible development of cavitation bubbles within the brain due to high negative pressure at the contrecoup site. The growth and subsequent collapse of these bubbles may induce local tissue damage.[5, 6]

A frequent cause of damage is the relative motion of the brain with respect to the skull. This is called *shear damage*. The brain is one of the softest biologic materials, shows nonlinear behavior, and changes properties in response to the applied loading rate.[7, 8, 9, 10] Composed mostly of water, brain material is resistant to changing its shape when subjected to either slow or transient pressures. However, brain tissue deforms easily when shearing forces are applied.[11]

Although TBI often has differing circumstances, three main types of mechanical loads have been described.

1. Impulse loading occurs when another area of the body sustains an impact and results in a rapid acceleration of the head.[12, 13, 14]
2. Translational acceleration loading occurs when the intracranial pressure becomes elevated in the opposite direction of contact generating stress waves which progressively increasing toward deep cerebral structures. [12, 13]
3. The mechanical loading which causes the most shear damage is e rotational acceleration of the parenchyma within the skull and bending/stretching of the craniospinal junction.[15]

Literature has also shown that when the rotational acceleration is produced in the coronal plane it is the most likely to produce loss of consciousness and damage within the deep internal structures of the brain.[16] However, experiments have shown that no matter the direction of the rotational acceleration, the regions of the cortex demonstrating the greatest damage were the infero-latereral aspects of the frontal lobes and temporal poles due to contact with the irregularly shaped skull.[17,18] High-level cognitive abilities in humans have been found to depend on the integrity of the prefrontal lobes. The vulnerability of the orbitofrontal and temporal poles following TBI is consistent with neuropsychological complaints of survivors, which include difficulty with executive function, memory.[19,20,18]

Diffuse damage that occurs during TBI encompasses diffuse axonal injury (DAI), cerebral swelling, cerebral ischemia and the resultant changes at the cellular level. DAI cannot always be seen through CT or MRI but is evident as widespread, microscopic changes to axons in 40% of all persons with severe TBI and is thought to be the most prevalent cause of neurologic disability. [21-24] The phenomenon of DAI includes the mechanical stretching of axonal cell membranes resulting in ionic flux, diffuse depolarization, calcium influx, and mitochondrial swelling. [25] This pathophysiologic process has been shown to result in eventual axonal disconnection. [26,27] The damage resulting from axonal disconnection was found to progress through cortical and subcortical structures over 4-6 weeks and the effect was correlated with impaired navigation in the Morris Water Maze in rodents, a sign of spatial learning and memory deficits.[26]

Diffuse damage also occurs following TBI due to the toxic cascade effects of inflammation and free radicals. Immediately after mechanical trauma to the brain, acceleration forces and deceleration forces initiate a complex cascade of neurochemical and neurometabolic effects (Fig. 1.2). This event begins with the disruption of the neuronal cell membrane and axonal stretching. The result of this disruption and stretching causes a surge of ions through previously regulated channels. From here the cascadeprogresses to calcium homeostasis failure, prolonged calcium elevations (leading to failure of ATPases), activation of proteases, formation of free radicals, outward flow of potassium ions, influx of sodium and water, excessive glutamate release and activation of

glutamate receptors, catastrophic mitochondrial depolarization, and activation of cytokines. [28] The glutamate channels have an especially strong association with learning, specifically long-term potentiation (LTP) and depression (LTD). Not surprisingly, LTP has been found to be impaired post-injury.[29-31]

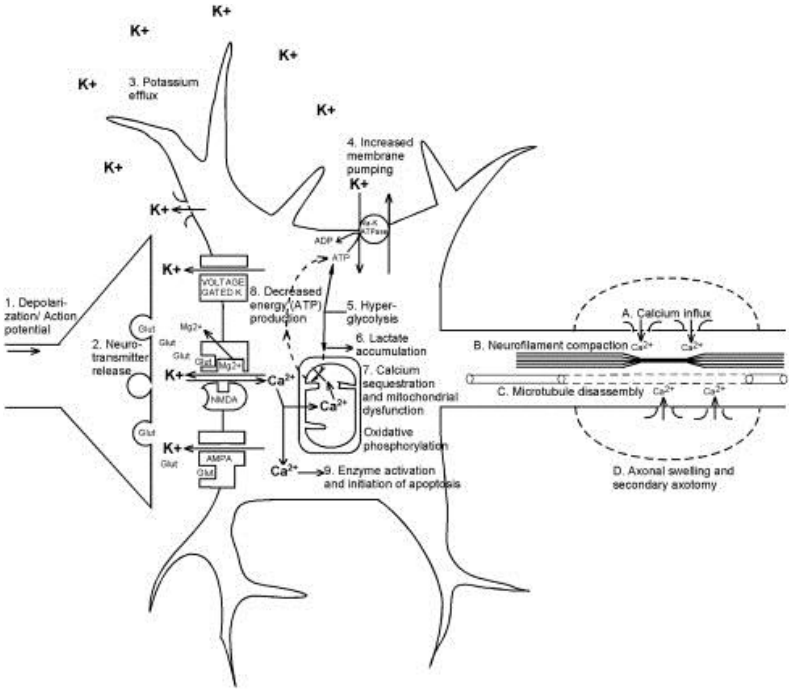

Figure 1.2. Neurometabolic cascade after traumatic injury. Cellular events: (1) nonspecific depolarization and initiation of action potentials, (2) release of excitatory neurotransmitters (EAAs), (3) massive efflux of potassium, (4) increased activity of membrane ionic pumps to restore homeostasis, (5) hyperglycolysis to generate more ATP, (6) lactate accumulation, (7) calcium influx and sequestration in mitochondria, leading to impaired oxidative metabolism, (8) decreased energy (ATP) production, (9) calcium activation and initiation of apoptosis. Axonal events: (A) axolemmal disruption and calcium influx, (B) neurofilament compaction via phosphorylation or sidearm cleavage, (C) microtubule disassembly and accumulation of axonally transported organelles, (D) axonal swelling and eventual axotomy. AMPA, d-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Glut, glutamate; NMDA, *N*-methyl-d-aspartate. [31]

Damage to the brain can also occur through extra-neurological systems such as hypotension, hypoxia, anemia and/or malnutrition following a TBI. The occurrence of an early hypoxic episode is strongly related to the level of consciousness because the

protective reflexes are lost when a patient's Glasgow Coma Scale (GCS) falls to 8 or below, increasing the risk of airway obstruction and aspiration. Literature has shown a relationship between early hypoxia and neuropsychological outcome, despite the substantial time interval between this secondary insult and the assessment.[32]

TBI can be devastating to the day-to-day functioning of survivors. Individuals commonly experience difficulty with memory, information-processing and executive processing.[33-36]Cognitive impairments resulting from the injury have been found to contribute to difficulties re-integrating into the community and include the challenge of returning to previous employment, education, premorbid family life and social relationships.[35-37] Even at 10 years post-injury, poorer functional outcomes were associated with impaired information processing, memory and executive function.[35]

It thereby becomes necessary to find new, evidence-based, clinically feasible interventions that will address these lasting cognitive deficits following TBI. To that end, considerable evidence exists to support the hypothesis that participation in an aerobic exercise program can serve to enhance working memory and executive function in both animals and. [38-50] And more specifically with TBI, Griesbach and colleagues demonstrated that brain-injured animals that participate in aerobic exercise not only performed better in a spatial memory task.[51-54] Thus, it is plausible that this intervention may also demonstrate the same improvements in a human, brain-injured population.

Based on extensive literature review and research, this three-part investigation examines

the effects of a 12-week aerobic exercise intervention on cognition and brain activity in moderate-to-severe TBI subjects.

1.2. Thesis Organization

Following the Introduction, this thesis is organized into three parts. Part one (Chapter II), is an extensive literature review related to the scientific promise and potential physiological mechanisms underlying aerobic exercise as a potential intervention to improve cognition following TBI. This literature review was initially published in the Journal of Head Trauma Rehabilitation 25(3):184-192, May/June 2010 by the author of this thesis.[55]

Parts two and three are two separate research reports written as Chapters III and IV. Each report was formatted for journal submission. Due to University Graduate School thesis formatting standards, the section written to open the chapter (manuscript) as a structured abstract could not be titled "Abstract". Therefore, chapters open under the subheading "Introductory Summary" (as suggested by the Graduate School). Finally, to meet Graduate School formatting standards, the thesis concludes by listing, in alphabetical order, all cited references.

The first study (Chapter III) reports cognitive changes in working memory, executive function, and the subject's (N=7) perceived function utilizing behavioral measures following participation in a 12-week aerobic exercise program. The second study

(Chapter IV) reports findings of the cortical changes in TBI subjects (N=7) following participation in a 12-week aerobic exercise program. Functional magnetic imaging (fMRI) data was gathered on the subjects during a working memory task prior to and following exercise program participation. Regions of interest in the cortex included the dorsolateral prefrontal cortex, anterior and posterior cingulate cortices, and the precuneus.

1.3. Aims and Hypotheses

Listed by Chapter, Study and Abridged Title.

Chapter III. Study 1. $_{(A)}$

Effect of Aerobic Exercise on Cognition Following Traumatic Brain Injury.

Aim 1. $_{A.1)}$ To examine effect of cardiorespiratory fitness training on cognition within chronic, moderate-to-severely injured TBI subjects. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H. 1.$_{A.1)}$ An improvement in everyday memory will occur as measured by an increase in total and subscale scores on the Rivermead Behavioral Memory Test – Extended Version (RBMT-E).

H. 2.$_{A.1)}$ An improvement in working memory will occur as measured by an increase in the number of items correctly completed on the Paced Auditory Serial Addition Test (PASAT).

H. 3.$_{A.1)}$ An improvement in executive function will occur as measured by the Wisconsin Card SortingTest (WCST-64, Computer Version 2

Research edition).

Aim 2. $_{A.2)}$ To examine the effect of cardiorespiratory fitness training on subject disability within chronic, moderate-to-severely injured TBI subjects. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H. 1.$_{A.2)}$ An improvement in subjects' disability will occur as measured by a decrease in overall score and three subscale scores (Ability Index, Adjustment Index, and Participation Index) on the Mayo-Portland Adaptability Inventory (MPAI).

Aim 3. $_{A.3)}$ To determine the extent of improvement in cardiovascular capacity of moderate-to-severe TBI subjects following participation in a 12-week aerobic exercise program. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.$_{A.1.)}$ An improvement in subject's aerobic capacity as demonstrated by a significantly greater VO_2 max as measured during a maximal graded treadmill test.

Chapter IV. Study 2. $_{(B)}$

Effect of Aerobic Exercise on Brain Activity Following Traumatic Brain Injury.

Aim 1 $_{B.1)}$ To ascertain the type of changes that occur in the cortical activity of

moderate-to-severely injured TBI subjects following participation in a 12-week aerobic exercise intervention. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1. B.1) A decrease in the fMRI voxel count indices and signal intensity within the dorsolateral prefrontal cortex (DLPFC) and precuneus to occur during the 2-back task.

H.2. B.1) A decrease in the fMRI voxel count index and intensity of the ACC and PCC to occur during all N-back tasks.

H.3. B.1) A more positive laterality index indicating greater left hemispheric involvement during all N-back tasks.

Aim 2. B.2) To determine the extent of improvement in cardiovascular capacity of moderate-to-severely injured TBI subjects following participation in a 12-week aerobic exercise program. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.B.2.) A significantly greater maximal oxygen uptake to occur during a maximal graded treadmill test as measured by an increase in VO_2 max.

Aim 3. B3) To determine the extent of working memory improvement in moderate-to-severely injured TBI subjects following participation in a 12-week aerobic exercise intervention. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.$_{B3.)}$ A decrease in reaction time to occur during the N-back tasks.

H.2.$_{B3.)}$ An increase in accuracy to occur during the N-back tasks.

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CHAPTER II

RELATIONSHIP BETWEEN AEROBIC EXERCISE AND COGNITION

Lojovich JM. The relationship between aerobic exercise and cognition: Is movement medicinal? *J Head Trauma Rehabil*. 2010; 25 (3):184-192.

Summary

Each year approximately 1.5 million individuals sustain a TBI. The result is often difficulties in memory and executive function which limit independence. Aerobic exercise not only has been found to impact cardiovascular systems, but has also shown benefits to brain function specifically in the domain of memory and learning. Recent evidence is shedding light on the mechanisms impacting cognitive performance following the participation in aerobic exercise. Literature has demonstrated increased hemodynamics within the brain, changes in neurotransmitters, and increased levels of brain-derived neurotrophic factor that stimulates neurogenesis and resistance to further injury. This review article explores the current literature and the possibility of exercise acting as an adjunct treatment to enhance the effectiveness of cognitive rehabilitation.

2.1. Introduction

Every year, 1.5 million individuals in the United States sustain traumatic brain injuries (TBI) and 5.3 million adults are currently living in the community with TBI.[1] Many of these individuals report chronic problems with concentration, memory, distractibility, forgetfulness and difficulty doing more than one thing at a time often leading to difficulties returning to work or school. [2] The largest group of TBI survivors is young adults in their prime working years, with 1 in 4 of all persons with brain injuries being unable to return to work, resulting in an estimated 56.3 billion annual cost for TBI care.[1] Investigations using brain imaging provide insight into the neural networks necessary for higher level cognition as well as changes in those networks following TBI. [3,4,5,6,7,8,9]

Interestingly, a recent body of evidence suggests that aerobic exercise could have beneficial effects on cortical function and specifically in areas associated with cognition. The purpose of this critical review of current and hallmark literature is designed to give an overview of the preliminary evidence related to the vascular, neurotransmitter and neurotrophic changes in the brain following aerobic exercise. The findings from this body of research provide a foundation to investigate the use of exercise as a rehabilitative intervention to improve cognitive function after TBI.

2.2. Cortical Function Following TBI

The participation of the dorsolateral prefrontal cortex (DLPFC) in executive function and working memory has been established in primates using single unit recordings and normal adults using positron emission tomography (PET) and functional magnetic imaging (fMRI).[10, 11, 12, 13, 14] Evidence from these studies has identified networks of working memory including bilateral frontal areas (Brodmann areas 44, 6, 8) and parietal activation with the addition of Brodmann areas 9 and 46. It is suggested that the inferior frontoparietal connections might mediate articulatory rehearsal where information to be remembered is repeated. Increased prefrontal activation was present during more difficult tasks like planning, and manipulating information indicating a greater demand on executive processing.

Neuroimaging studies following TBI have consistently supported the idea of prefrontal cortical dysfunction often without evidence of structural brain lesions in the region.[7, 8] In

a study of subjects with mild TBI and no evidence of lesion through neuroimaging, TBI subjects showed a more diffuse pattern of cortical activation and load related differences during an auditory N-back task compared to uninjured controls. The N-Back task is a frequently used instrument to measure working memory. This test requires codification, temporary storage and response, for the individual to update and maintain information continuously. The stimuli are presented at regular intervals and the subject is asked to remember the digit 1, 2 or 3 back from the current stimuli. As processing load increased during the study, TBI subjects showed a relatively minimal increase between the relatively easy 0-back and 1-back conditions and instead demonstrated a significant and disproportionately large increase in activation compared to controls, especially in the right DLPFC and parietal cortices (Fig. 2.1). [3, 4, 5]

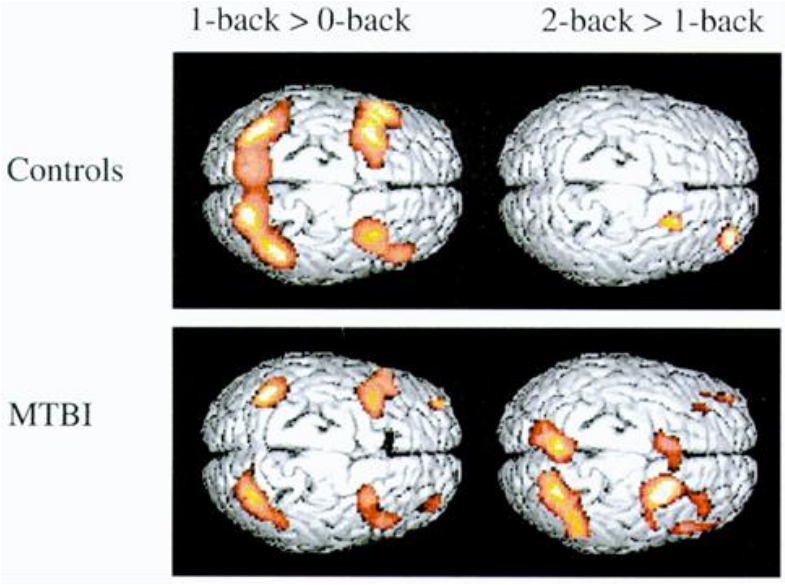

Figure 2.1. The gyri location of activations (bilateral dorsolateral prefrontal and superior parietal) were similar in both groups from the 0-back to 1-back condition. Major differences, were observed in the 1-back to 2-back comparison. Note the more extensive activation of primarily right superior parietal and dorsolateral prefrontal cortex in patients with mild traumatic brain injury (MTBI).[3]

Similarly, an fMRI study of individuals with moderate-to-severe brain injury using the paced auditory serial addition task (PASAT) found patterns of activation that differed from age matched controls, with greater error rates in the cognitive task. [6] During the working memory task, brain activation was located primarily in the middle frontal and temporal gyri in both the TBI subjects and controls. However, when data were analyzed using an index of dispersion and laterality, TBI subjects showed an extensive increase in the dispersion of the working memory neural network (Fig. 2.2).

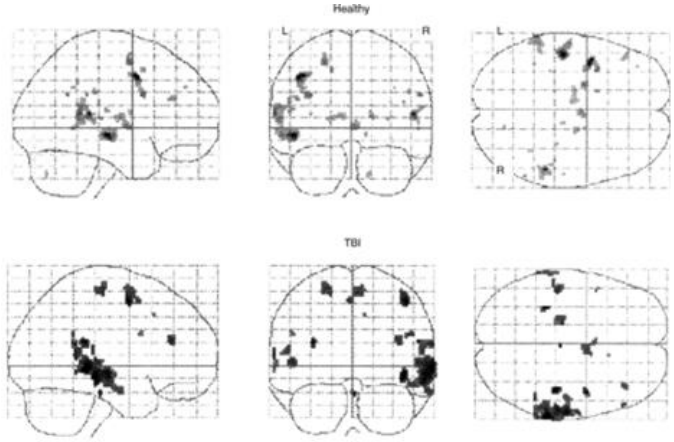

Figure 2.2. Group activation patterns on the working memory task for the TBI (n=9) and healthy control (n=7) groups. Maximum intensity projections in the three orthogonal views of the brain (sagittal, coronal, and axial) depict areas of significant activation.[6]

TBI subjects also demonstrated a greater lateralization to the right hemisphere compared to the control group unrelated to the primary areas of damage (Fig. 2.3). In uninjured adults, working memory cortical activation has been shown to be very tightly concentrated. However, in the TBI subjects the activation. Although in similar areas activation in TBI subjects was far more scattered, potentially indicating a decrease in the

efficiency of the neural network.

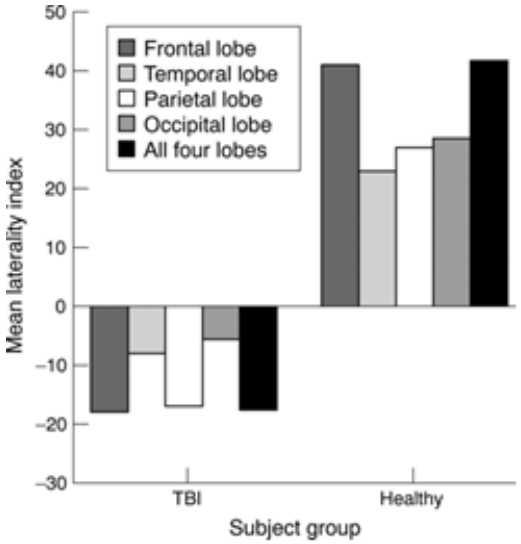

Figure 2.3. Mean laterality index scores for each group separated by lobe, indicating degree to which cerebral activation was lateralized during performance of the PASAT (positive scores indicate more left hemispheric activation, negative scores represent more right sided activation).[6]

Soeda et al., (2005) has further expanded on the variations between TBI and normal activation patterns during cognitive tasks by demonstrating not only prefrontal activation differences, but alterations in the activity of the anterior cingulate cortex (ACC). [9] The caudal portion of the ACC is functionally implicated in complex cognitive/attentional processing and conflict resolution (the ability to make a decision between conflicting choices) and is closely connected to the activity in the prefrontal cortices. [15] In the study by Soeda et al., subjects with severe TBI were compared to age-matched controls during tests of selective attention and working memory utilizing a modified Stroop task. fMRI results again showed a more dispersed and diminished activation pattern in the prefrontal and parietal cortices, as well as a decrease in the overall activity of the caudal ACC (Brodman's area 24 and 32) compared to the neurologically intact control subjects.

These findings appear to be associated with the results of diffuse axonal injury and the decrease in the connectivity of the prefrontal, parietal, and ACC regions.
Overall, the number of studies and the underlying functional correlates regarding patterns of TBI prefrontal and anterior cingulate activity compared to uninjured controls is limited. However, current literature is consistently suggesting that alterations in prefrontal and anterior cingulate activity do occur across tasks and TBI severity compared to normal controls.

The TBI literature regarding physiologically enhancing cognition is limited. Current efforts to rehabilitate cognition in the TBI population rely primarily on a combination of education, social support, practice, process training, and compensation with an assistive device for memory or pharmacological agents. [16, 17, 18] Current efforts to rehabilitate cognition following TBI often show varied results. TBI survivors, their caregivers, and their employers/educators often have continuing complaints regarding concentration, distractibility, forgetfulness and mental flexibility following conventional treatment. These residual deficits indicate an ongoing need to enhance the efficacy of cognitive rehabilitation for this population. Aerobic exercise is one alternative and potential adjunct to standard cognitive rehabilitation showing promise in both animal and human subjects is the use of aerobic exercise.

2.3. Aerobic Exercise and Cognition

Through contemporary studies, it is now becoming clear that exercise not only improves

overall cardiovascular and metabolic health but also may have the potential to improve neurobiological processes and functions within the brain. Cardiorespiratory deconditioning is a common side effect for survivors of TBI as a result of prolonged bed rest, physical impairments, lack of initiation and depression. [19, 20] In Mossberg's (2007) study of aerobic capacity following TBI in comparison to sex and age-matched controls, individuals with TBI demonstrated significantly lower peak responses for heart rate, VO2, VE, oxygen pulse and submaximal VE/ VO2.[20] It has been suggested that decreased peak VO2 has been associated with fatigue and employment productivity, further limiting TBI survivors from community re-entry.[21] Although the benefits of cardiovascular health in the TBI population is an important feature of aerobic exercise, the possibility of aerobic exercise also influencing cognitive function could be even more valuable.

Much of the research regarding exercise and cognition in humans has focused older adults. In a 6-year, longitudinal study of 349 older adults, the neuroprotective effects of exercise were demonstrated by a positive correlation between good cardiovascular fitness and high measures of global cognitive function. [22] This finding was echoed in a study by Weuve et al. (2004), who studied a group of women from 1986-1995 and found that higher levels of physical activity were correlated with better cognitive performance in conjunction with diminished cognitive decline over time. [23]

Intriguingly, older adults have also been found to have the greatest losses in the frontal,

prefrontal and temporal regions, similar to the cortical areas most often damaged following TBI. [24] In a study of 124 well elderly, randomized to either a walking group or a toning/control group, Kramer et al (1999) showed significant improvement in the executive control processes of planning, scheduling, inhibition, and working memory. [25] Interestingly, the beneficial cognitive effects of aerobic exercise were selective. Aerobic exercise did not significantly affect the subjects' performance on other cognitive measures unrelated to frontally mediated executive function. [25] Similarly, in a study examining 29 community dwelling older adults, Colcombe et al. (2004) investigated the effects of increasing cardiovascular fitness on prefrontal and ACC plasticity in the aging brain.[24] Subjects were randomly assigned to participate in either a progressive aerobic fitness group or a stretching and toning (control) group for 45 minutes, 3 times per week for 6 months. As expected, VO2 max was significantly increased in the aerobic exercise group. In the cognitive measures of attention and working memory the control subjects demonstrated only a 2% reduction in reaction time (RT) compared to the aerobic exercise group's decrease of 11%, suggesting improvement in the subject's speed of processing. Following the 6 month intervention, the aerobic group also showed significantly increased activity in cortical areas associated with cognition including the right medial frontal gyrus (BA 46), superior frontal gyrus (BA 8), and superior parietal lobe (BA 40). Within the aerobic exercise group, there was a significant decrease in activity in the ACC to a level more consistent with neurologically intact young adults. This pattern of activation appears to be associated with a decreased need for the complex problem solving and conflict resolution capabilities of the ACC and a sole reliance on the medial

frontal gyrus and parietal lobe for the cognitive task (Fig 2.4). [24]

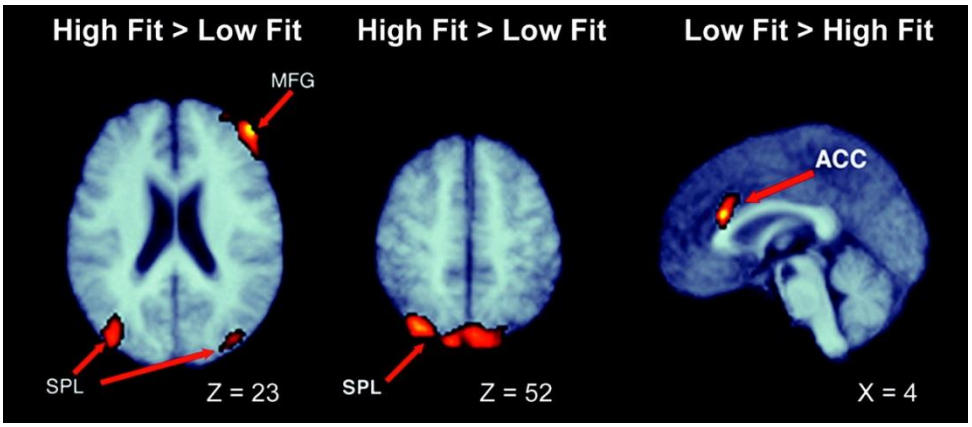

Figure. 2.4. Demonstrates changes in brain activity between community dwelling older adults following participation in either an aerobic exercise or non- aerobic group.[24]

In the clinical studies above, the benefit of aerobic exercise and its effect on cortical activity, learning, and memory have been clearly identified. The next focus of research has been to explore the therapeutic potential of aerobic exercise following cortical injury. To understand this question, the underlying structural and molecular pathways explaining the behavioral findings of clinical studies need to be delineated.

The physiologic reasons for functional improvements in cognition following aerobic exercise have primarily focused on three hypotheses. The first hypothesis suggests that aerobic exercise produces vascular changes including an increase in oxygen saturation, promotes angiogenesis, and increases cerebral blood flow in areas related to cognitive function. [26, 27, 28, 29] The second hypothesis proposes that changes in neurotransmitters

may be responsible for the behavioral changes in cognition. And finally, the most prominent hypothesis surrounds the abundance of literature demonstrating an increase in neurotophic factors as a result of exercise. Neurotrophins such as brain derived neurotrophic factor (BDNF), insulin-like growth factor (IGF), and nerve growth factor (NGF) are endogenous proteins that have been described as factors that regulate the proliferation and differentiation of cells in the developing central nervous system (CNS). [30] BDNF in particular has been implicated in many beneficial neurologic processes including neurogenesis, synaptogenesis, dendritic branching, and neuroprotection.

2.4. Vascular Changes

As early as 1980, Spirduso speculated on the possibility of enhanced cerebral blood flow (CBF) as a potential mechanism for the changes in cognition as a result of regular physical activity. [31] Recent advances in the study of cerebral circulatory responses to exercise now allow researchers to gain information regarding the blood flow in specific vessels and hemispheres, cerebral tissue oxygenation, flow velocity, and cerebral metabolism. [11, 32, 33, 34] Ultimately, the goal of cerebral circulation is to meet the metabolic needs of the brain and maintain homeostasis through the removal of waste products. While global CBF remains stable between rest and moderate exercise, findings from both animal and human studies indicate regional CBF can increase up to 30% from rest to maximal exercise levels. Vessels showing a particular increase in CBF in response to exercise are the middle and anterior cerebral arteries. These arteries

supply the prefrontal, frontal, temporal, and portions of the parietal lobes.[35, 36] The CBF changes reported in these studies, however, are transient in nature and have primarily measured hemodynamic effects during exercise.

Angiogenesis is defined as the formation or sprouting of new blood vessels by pre-existing mature endothelial cells. [37] Angiogenesis occurs spontaneously during brain development, but diminishes with increasing age. [38] Black et al. (1990) was one of the first to demonstrate more lasting effects in CBF as a result of long-term exercise, showing an increase in capillary density and perfusion in the primary motor cortex (M1) of rats, and subcortical areas such as the hippocampus. [26] Since the hippocampus is a highly oxygen dependent structure instrumental in the development of new memories, angiogenesis may be one explanation of the improved learning and memory found following aerobic exercise. The finding of increased blood vessel density within the adult central nervous system (CNS) after consistent exercise has been often reproduced in animal models (Fig. 2.5). [28, 29, 37, 39] Although there is extensive research to be done to establish the significance of angiogenesis as a result of exercise, the possibility exists that angiogenesis produces a long-term increase in CBF or oxygen utilization that may significantly affect brain function and improvements in memory.

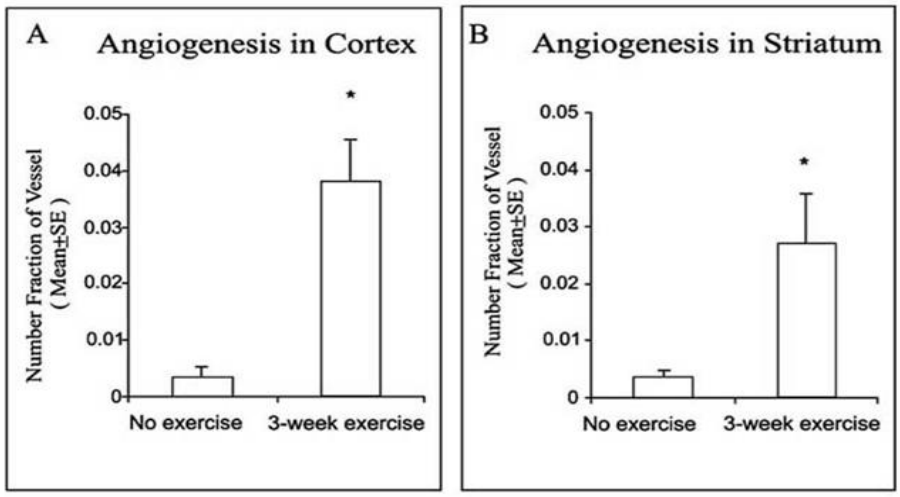

Figure. 2.5. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise.[26]

2.5. Neurotransmitter Changes

It has long been asserted that when animals participate in exercise, a biochemical response occurs within the body and the brain. Experiments have shown that exercise increases serum calcium levels. Increased calcium can then be transported to the brain to activate the rate limiting enzyme for catecholamine (dopamine and norepinephrine) synthesis (Fig 2.6). [40] Both dopamine and norepinephrine are neurotransmitters found to have significant involvement in human cognitive performance. Sutoo and Akiyama (1996) compared sedentary adult male mice to a group of mice forced to run for 15 to 120 minutes at a speed of 20 meters per minute. [40] Serum calcium levels in the exercise group were 7-18% higher than in the sedentary controls. Dopamine levels in the neostriatum were also 31% higher. [40] Exercise changes neurotransmitter concentrations, but also stimulates differences in neurotransmitter receptors and transporters. Molteni et al. (2002) looked at differences in the effects of both acute and chronic exercise in rats by

measuring hippocampal gene expression of receptors and transporters at 3, 7, and 28 days of exercise. [41] Findings showed that after 3 and 7 days of exposure to a running wheel, rats demonstrated increases in NR-2A, a glutamate receptor within the hippocampus. It was also found that acutely (3 days), EAAC1 was increased. EAAC1 is a glutamanergic transporter responsible for removal of extracellular glutamate from the synapse. Interesting as these findings are, implications are as yet unclear. However, it is possible that these changes in receptors and transporters may have a role in neuroprotection prior to injury or diseases of the brain reported in the exercise literature.

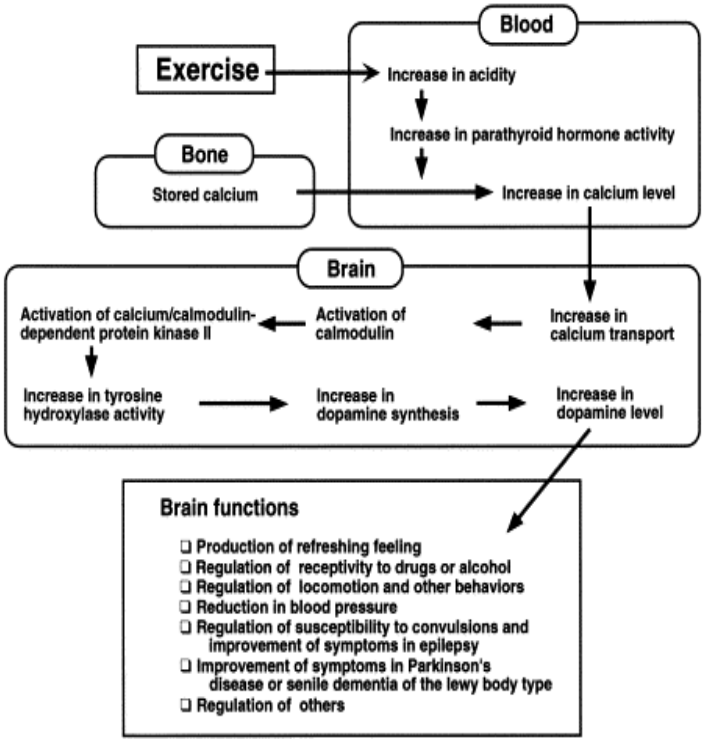

Figure. 2.6. Physiological explanation of the effects of exercise on dopamine.[40]

2.6. Neurotrophin Changes

Exercise has also been linked to molecular contributions from neurotrophins, intercellular substrates that are implicated in altering structure and function within the brain. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is implicated in the differentiation, extension, and survival of neurons in the hippocampus, cortex, striatum, and cerebellum during development. Itis also thought to increase the brain's resistance to damage and degeneration with aging. [42] BDNF has also been reported to presynaptically potentiate hippocampal neurons by increasing the levels of synaptophysin and synaptobrevin, which assist in the docking and fusion of neurotransmitter vesicles. [43] Synapses with more docked vesicles ultimately respond better to high frequency tetanic stimulation, thereby leading to enhanced long term potentiation (LTP) and learning. Tyler and Pozzo-Miller (2001), injected BDNF directly into the rat hippocampus. Upon histological analysis, BDNF increased the number of docked vesicles in the dendritic spines of the CA1 area of the hippocampus and produced a larger quantity than normal of neurotransmitter release. The increase in neurotransmitter release eventually lead to an increased frequency of excitatory post synaptic potentials (EPSPs).[44] Due to the increase in the frequency of EPSP's there was also increased dendritic growth and spine density, thereby increasing the number of future synapses. [44, 45] In a quickly growing body of literature, regulation of BDNF has been clearly shown to be activity dependent. This is evidenced by increased BDNF gene expression (BDNF mRNA) as a result of running. [46, 47] The area demonstrating the greatest increase in BDNF mRNA in rodents is the hippocampus, a structure associated with memory and cognition rather than the motor

cortex, striatum or cerebellum, associated with motor. [46, 47] In an early study by Neeper (1995), rats were put either in a sedentary group or a group with access to a running wheel. In the analysis, increased BDNF mRNA was found in the hippocampus as well as the caudal 1/3 of the neocortex (Fig. 2.7). [47, 48] Interestingly, there was also a positive correlation between BDNF mRNA levels and the distance run by each rat. [47]

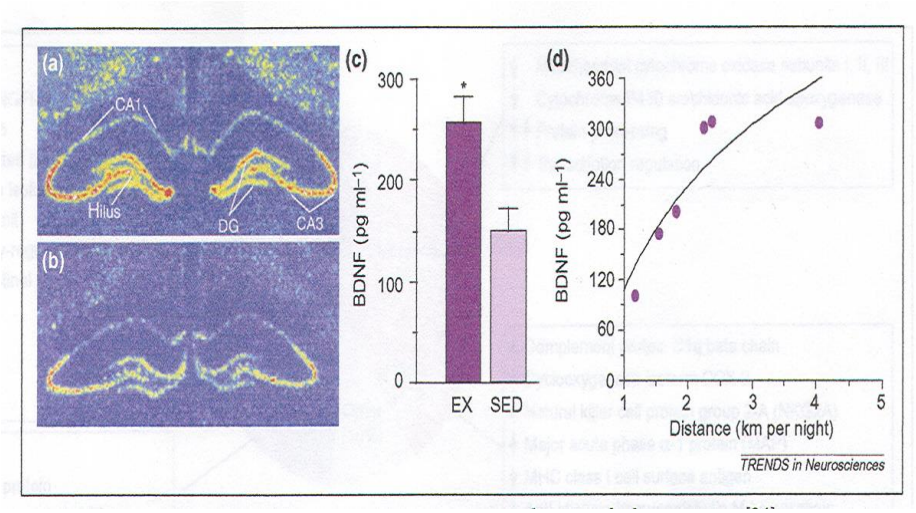

Figure. 2.7. Landmark study demonstrating the increase of BDNF in the hippocampus of mice allowed to run compared to non-running mice.[47]

Animals raised in enriched, complex environments with items to manipulate, novel foods, social interaction, and other stimulating activities have also demonstrated increased BDNF resulting in synaptogenesis, a greater density of synapses, increased dendritic branching, neurogenesis and neurochemical changes compared to sedentary animals. These neuronal changes not only produce immediate improvements in cognition as measured by the Morris Water Maze, a test of memory for rodents, but appear to be neuroprotective as well. [26, 39] Since many of these studies utilized a running wheel as a

component of their enriched environment, the effects of exercise independent of other environmental enrichments needed to be delineated. van Praag et al. (1999) compared mice in four groups given access to a running wheel, other stimulating enrichments, a learning task, or standard housing. [45, 48] Results showed neurogenesis and significantly improved cell division within the hippocampus of the running wheel group. Increases in BDNF as a result of exercise, have also been demonstrated in a few studies using human subjects of normal functioning college age students. In a study of the acute effects of exercise by Ferris et al., (2007), subjects performed a graded exercise test on 2 separate days. One was at 20% below the subjects' ventilatory threshold (Vth) and one at 10% above their Vth. [49] The subjects' serum BDNF and lactate from the antecubital vein, and the Stroop color, and word test were measured following participation in the exercise test. BDNF values and the cognitive measure of the Stroop task increased significantly following the graded exercise test at 10% above the Vth only. [49] It was also found that the changes in BDNF did not correlate with VO2 max or the changes in cognition, but did positively correlate with changes in lactate. This finding suggests that higher exercise intensity may be necessary to produce changes in BDNF.

BDNF has been tied not only to neurologic changes in the human brain, but also behavioral measures of cognitive function. In a study by Komulainen et al.(2008), the amount of serum plasma BDNF was shown to be a significant biomarker for decreased memory and general cognitive decline in aging women. Women with a higher mean of serum BDNF demonstrated significantly better scores in the Mini Mental State

Examination, Word List Memory, Naming Test, Word List Recall, Word List Recall and Word List Memory. [50]

The role of activity induced BDNF following brain injury was examined though recent studies of TBI rats. [51, 52, 53, 54, 55] In this series of experiments, the rodents underwent either a lateral fluid percussion injury or a sham surgery procedure as a control. Not surprisingly, the rats with the TBI were significantly more impaired in their spatial memory in the Morris Water Maze than the sham surgery rats. Tissue sample analysis found the animals with TBI demonstrated a significant decrease in BDNF in the ipsilateral hippocampus, seemingly associated with the spatial memory deficits seen in the water maze. When BDNF was exogenously infused into the hippocampus of rats with TBI, neuromotor function, learning memory or neuronal loss was unaffected. However, when BDNF was endogenously increased by exercise in rats sustaining a TBI, the animals demonstrated significant cognitive improvements in the Morris Water Maze. [55] In another study by Griesbach et al., (2004 and b), on the effects of exercise on mice with TBI, animals were stratified into either a sedentary group or given access to a running wheel. [52, 54] Again, there was an increase in BDNF levels in the sham exercise animals compared to the sham sedentary animals, as well as the TBI exercise animals compared to the TBI sedentary animals. In this experiment, there was also a positive correlation between the upregulation of BDNF and the distance each animal ran.

Follow-up experiments utilizing the same methodology to investigate the optimal time post-injury to initiate exercise to enhance BDNF output in animals have also been studied. [52, 53, 54]

Results have demonstrated that there is indeed a therapeutic window for the implementation of aerobic exercise that is dependent on injury severity. In adult male rats with mild fluid percussion injuries, significantly increased BDNF levels and improved performance on the spatial learning task were only evident in the group that was allowed to exercise 14-20 days post-injury. [52] In moderately injured rodents, improvements in BDNF and performance were only shown in the group allowed to exercise from post-injury days 30-36. [54] The acutely exercised rats in all of the studies did not demonstrate the upregulaton of BDNF and consistently performed worse on the Morris Water Maze compared to the delayed exercise, sedentary and the sham groups. This finding may be due to the increase metabolic demand that exercise entails during a time of neurochemical and metabolic disruption. The finding that the therapeutic use of aerobic exercise is potentially time and severity dependent should give pause to the premature, post-injury use of exercise since the brain may still be compromised. (Fig. 2.8)

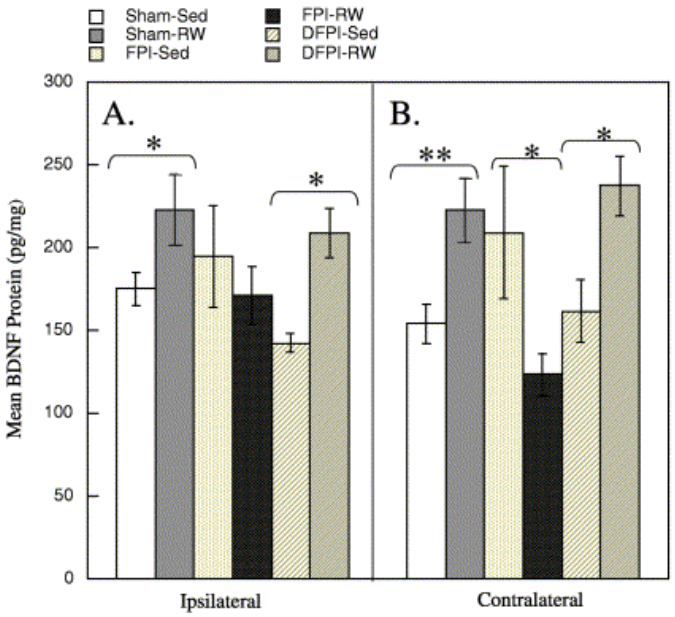

Figure. 2.8. Effects of exercise in sham and TBI rats housed with or without access to a RW from post-injury days 0–6 (acute) or 14–20 (delayed). BDNF protein levels within the hippocampus (FPI vs. Sham), (acute vs. delayed) and exercise: (RW vs. Sed)]. [51]

2.7. Summary and Conclusions

The goal of this chapter is to identify potential rehabilitative strategies for TBI patients with higher functional abilities who still struggle with return to everyday activities, school, and work. In the course of this literature review, it becomes apparent that aerobic exercise has the capacity to promote functional changes within the brain and cognition. More specifically, aerobic exercise has the capacity to change areas of the brain and their cognitive domains that are particularly susceptible to the effects of a traumatic brain injury, such as attention, working memory, executive function, and conflict resolution. The underlying vascular, biochemical and structural mechanisms behind the behavioral changes related to aerobic exercise also becomes clearer with each progressive investigation. Aerobic exercise has been found to aid in the development of new

vasculature, promote changes in neurotransmitter levels and effectiveness, and also lead to increases in BDNF thereby producing neurogenesis and synaptogenesis. These findings show that aerobic exercise could be implemented into the regular routine of TBI survivors to promote a higher level mobility, a healthy lifestyle and to battle losses in endurance post-injury. Although investigations of the physiological and behavioral effects of aerobic exercise on cognition are compelling, it is still too soon to conclusively state a cause effect relationship in survivors of TBI. It now becomes necessary to research aerobic exercise as a potential rehabilitative strategy to enhance cognition in brain-injured human survivors.

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CHAPTER III.

EFFECT OF AEROBIC EXERCISE ON COGNITION FOLLOWING TRAUMATIC BRAIN INJURY

Summary

In the previous literature review (Chapter II), the mechanisms impacting cognitive performance following aerobic exercise were explored. Emerging evidence suggests that exercise may in fact improve cognitive function in animals, older adults, CVA and Alzheimer subjects. The purpose of this preliminary clinical study was to describe changes in the everyday memory, working memory and executive function in individuals with moderate-to-severe chronic traumatic brain injury (TBI) following participation in a 12-week aerobic exercise intervention. **Methods:** A single group, pretest-posttest design was used. Seven males with moderate-to-severe TBI (mean age = 44.43 years, SD ±13.0), mean time since TBI (11.29 years, SD ± 11.12) completed a 12-week aerobic exercise intervention for 3 days per week. Primary outcome measures examined changes in everyday memory, working memory, executive function and perception of disability. Secondary measures examined changes in aerobic capacity (VO_2 max). A nonparametric Wilcoxon Signed-Ranks test was utilized to assess the differences between the subjects' aerobic capacity and cognitive test data prior to and following the exercise intervention. **Results:** Following the aerobic exercise intervention, significant improvements were found in the overall Rivermead Behavioral Memory Test (P = .016), Paced Auditory Serial Addition Test (PASAT) for both slower speed (P= .016) and faster speed (P= .031), and the Ability (P =.016), Adjustment (P =.016) and overall score (P =.013) of the Mayo-Portland Adaptability Inventory – 4. Aerobic capacity (VO_2 max) also significantly improved over the 12-weeks (P = .016). A significant correlation (r = -.75, P=0.05*)* between the subjects' change in aerobic capacity and improvement in the

amount of non-perseverative errors on the Wisconsin Card Sorting Test was also found. **Discussion:** This study is the first to examine the effects of exercise as an intervention to address the cognitive deficits that commonly persist following TBI. The results of this study indicate that a 12-week aerobic exercise intervention was associated with improvements in measures of everyday memory, working memory and perception of disability in subjects with moderate-to-severe chronic TBI. Limitations of this study include a small sample size and lack of a control condition. **Conclusion:** These results indicate the need for future study in the TBI population with a randomized control trial to further explore the benefits of aerobic exercise as an adjunct intervention to improve not only cardiovascular fitness but cognition and functional outcome. **Key Words:** Cognition, Memory, Executive Function, Exercise, Brain Injury.

3.1. Introduction

TBI survivors commonly experience continuing problems with cognition, including slow processing speed, poor attention, decreased working memory and impaired executive function.[1,2] On average these cognitive impairments tend to show some recovery within 1 year of injury. However, even up to 10 years post-injury, many survivors of moderate-to-severe TBI still exhibit significant problems with processing speed, memory and executive function.[2] Cognitive difficulties following TBI have also been associated with problems reintegrating into the community, including employment, education, family life, and social relationships.[3, 4] These collective components of community reintegration are commonly referred to as "productivity".[5,6]

Studies by Green et al. (2008) and Spitz and Ponsford (2012) found that the specific cognitive domains of working memory and executive functions were most strongly associated with and demonstrated the greatest significant impact on productivity following TBI.[5,6] One of the earliest models of working memory proposed a tripartite model of working memory.[7] In this model, two non-executive slave systems (the phonological loop and visuospatial sketch-pad) provided rehearsal and temporary storage while the central executive managed attentional control.[8] It is thought that working memory supports many higher cognitive functions by keeping a small number of items available in a state of active neural representation.[9] Working memory also requires the flexibility to highlight momentarily relevant items, enter new items, or discard those no longer needed. This is especially important for monitoring and manipulating information which are building blocks for executive function.[10,11, 12] Many studies also suggest a close association between working memory and attention, including shared capacity limitations and a common neural organization.[13,14, 15]

Bledowski, Rahm and Rowe (2009) found dissociable neural mechanisms of selection and updating attentional focus.[16] At any given time, there are numerous representations from the external environment or long-term memory within the working memory system. The mechanism of "selection" means that one item gains a privileged state of activation. This privileged state of activation is termed the "Focus of attention".[9,16] Therefore, situations that require switching between different items depending on their relevance require two processes working hand in hand. These dual mechanisms are the selection

process that activates to retrieve relevant information from working memory and the other mechanism focuses attention.[16] These two processes are sub-served by different sets of fronto-parietal cortical regions with independent behavioral roles. This theory is further supported by the fMRI and DTI findings that two distinct networks have been found to work in a paired way to support cognition. One network is task positive, and therefore activates during a cognitively demanding task, while another de-activates during attentionally demanding tasks (default mode network) to assist with focusing attention.[11] Executive functions may be defined as a group of higher-order integrative processes by which people monitor, manage and regulate the orderly execution of goal-directed activities of daily living (ADLs').[17]

According to the Joint Committee on Inter-professional Relations between the American Speech-Language-Hearing Association (ASHA) and Division 40 (Clinical Neuropsychology) of the American Psychological Association (APA), the cognitive domain of executive function includes all of the following behaviors: planning, task setting, goal formation, initiation of behavior, allocation of attentional resources, impulse control, maintenance, cognitive flexibility, self-awareness, self-regulation . Problems with these behaviors are also a common area of cognitive dysfunction following TBI.[18] It has been proposed that executive function is at mid-level of the hierarchical framework in which the results of executive activities (planning, problem solving, reasoning, etc.) are relayed to lower level systems (e.g., memory, comprehension). It is within these lower level systems where updating can occur.[19] "Metacognition" (or thinking about your

thinking) is located at the highest hierarchical level and includes self-awareness, self-monitoring and self-control of cognition while performing an activity.[20] This highly complex behavior is thereby a byproduct of a complex, integrative executive function system that includes a set of skills as opposed to a single skill.[20]

The dorsolateral prefrontal (task positive) circuit includes interconnections between the DLPFC, caudate, globus pallidus and ventro-anterior thalamus. This circuit is thought to be the most likely location associated with executive function since it is critical for providing top-down signals that modulate incoming sensory stimuli as information undergoes progressively more elaborative processing within association cortex.[19,21,22] Unfortunately, this circuit is susceptible to damage following TBI, especially the prefrontal cortex. This damage often results in ongoing struggles and limitations in returning to productivity.

Since the goal of rehabilitation specialists in TBI is to optimize a return to productivity, improving cognition is often the focus of rehabilitation efforts. According to the Cognitive Rehabilitation Task Force of the American Congress of Rehabilitative Medicine Brain Injury Special Interest Group, a systematic review of literature reveals that current practice standards to rehabilitate memory following TBI combine memory strategy training and the use of external memory compensations.[23] Although the studies within this systematic review demonstrate improvements in memory, functional magnetic imaging (fMRI) changes with cognitive rehabilitation continue to be mixed, showing

changes in some subjects but not others. These findings -- plus the continuing complaints of TBI subjects regarding concentration, distractibility, forgetfulness and mental flexibility -- indicate a continuing need to strive toward improving the efficacy of cognitive rehabilitation within this population.

The theory that aerobic exercise is linked to improvements in cognition is biologically plausible and supported by both behavioral and brain literature. Literature has now shown that aerobic exercise benefits brain vasculature through promoting increased capillary density and angiogenesis in the cortex.[24-28] Aerobic exercise has also been shown to produce an effect on the dentate nucleus of the hippocampus, which has been implicated in long-term potentiation and learning. The dentate nucleus of the hippocampus is closely linked to the prefrontal lobes and working memory.[29-31] Brain-derived neurotrophic factor (BDNF) has been shown to increase in this particular area in both neurologically intact and TBI animals following exercise.[32-39] BDNF has been implicated in neurogenesis (new neuron growth), enhanced neuronal survival, and synaptogenesis (development of new synapses).[32,36,40-45] Aerobic exercise has also been shown to produce behavioral improvements in memory and executive function in neurologically intact humans.[46-50]

Only a few studies have investigated the result of exercise intervention on cognition in people with cognitive impairments. A meta-analysis study exploring exercise outcomes in cognitively impaired individuals with dementia suggested that they exhibit a response to exercise similar to those who are cognitively intact.[51] In addition, a recent 12-week

exercise intervention study by Kluding et al., 2011 with CVA subjects showed similar behavioral improvements in tests of working memory and executive function.[52] To my knowledge, there have been no studies of the effect of aerobic exercise on cognition in persons with TBI. TBI is considered to be a difficult and problematic population in which to perform experimental research due to the variability in the mechanism of injuries, the diversity in the location of the injury within the brain, and the unreliability of subjects due to cognitive and behavioral issues. However, the need for interventional research within the TBI population is very real due to the impact it could potentially have on these individual's functional outcome and care cost. To this aim, the primary purpose of this preliminary clinical study was to describe changes in measures of executive function, day-to-day memory and working memory in individual subjects with chronic moderate-to-severe TBI following participation in a 12-week aerobic exercise intervention. We also assessed the influence of exercise on the secondary measures of aerobic capacity and the subjects overall disability. From a practical perspective, knowing whether the benefits of aerobic exercise already seen within animal, healthy, stroke and Alzheimer's Disease populations applies to TBI subjects may eventually lead to the clinical use of aerobic exercise programs as an efficacious adjunct to cognitive rehabilitation.

The aims and hypotheses for this study include the following;

Aim 1. A.1) To examine effect of cardiorespiratory fitness training on cognition within chronic, moderate-to-severely injured TBI subjects. Following participation in a 12-week

aerobic exercise intervention, I hypothesize:

H. $1._{A.1)}$ An improvement in everyday memory will occur as measured by an increase in

total and subscale scores on the Rivermead Behavioral Memory Test – Extended Version (RBMT-E).

H. $2._{A.1)}$ An improvement in working memory will occur as measured by an increase in the number of items correctly completed on the Paced Auditory Serial Addition Test (PASAT).

H. $3._{A.1)}$ An improvement in executive function will occur as measured by the Wisconsin Card SortingTest (WCST-64, Computer Version 2 Research edition).

Aim 2. $_{A.2)}$ To examine the effect of cardiorespiratory fitness training on subject disability within chronic, moderate-to-severely injured TBI subjects. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H. $1._{A.2)}$ An improvement in subjects' disability will occur as measured by a decrease in overall score and three subscale scores (Ability Index, Adjustment Index, and Participation Index) on the Mayo-Portland Adaptability Inventory (MPAI).

Aim 3. $_{A.3)}$ To determine the extent of improvement in cardiovascular capacity of moderate-to-severe TBI subjects following participation in a 12-week aerobic exercise program. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.$_{A.1.)}$ An improvement in subject's aerobic capacity as demonstrated by a significantly greater VO_2 max as measured during a maximal graded treadmill test.

3.2. Methods

3.2.1. Study Design

This study utilized a single-group, pretest – posttest design. IRB approval was obtained through The University of Minnesota, the Minneapolis Veteran's Administration Medical Center, and Healtheast Bethesda Hospital. A further assessment of the subject's decision-making capacity was determined through a Modified Dysken Screening Tool (Appendix 1). The assessment tested whether the subjects could both understand and provide informed consent. Per IRB recommendation, potential research subjects were required to answer at least 70% of questions correctly in order to have sufficient understanding of the study to provide informed consent. All seven subjects were legally competent and were able to understand the consent form as determined by the screening tool.

3.2.2. Subjects

A convenience sample of seven TBI adult males (mean age 44.4 years, SD ±13.0, range 28-60 years, mean total years of education 13.57 ±1.4, range 12-16 years) were recruited from the Minneapolis Veteran's Administration Medical Center in Minneapolis, MN, and Healtheast Bethesda Hospital in St. Paul, MN. Subjects were recruited through posted

flyers and brochures, therapist recommendation, and via a letter sent to Minneapolis VA TBI clinic participants. A CONSORT flow table (Figure 3.1) describes the subject recruitment and participation.

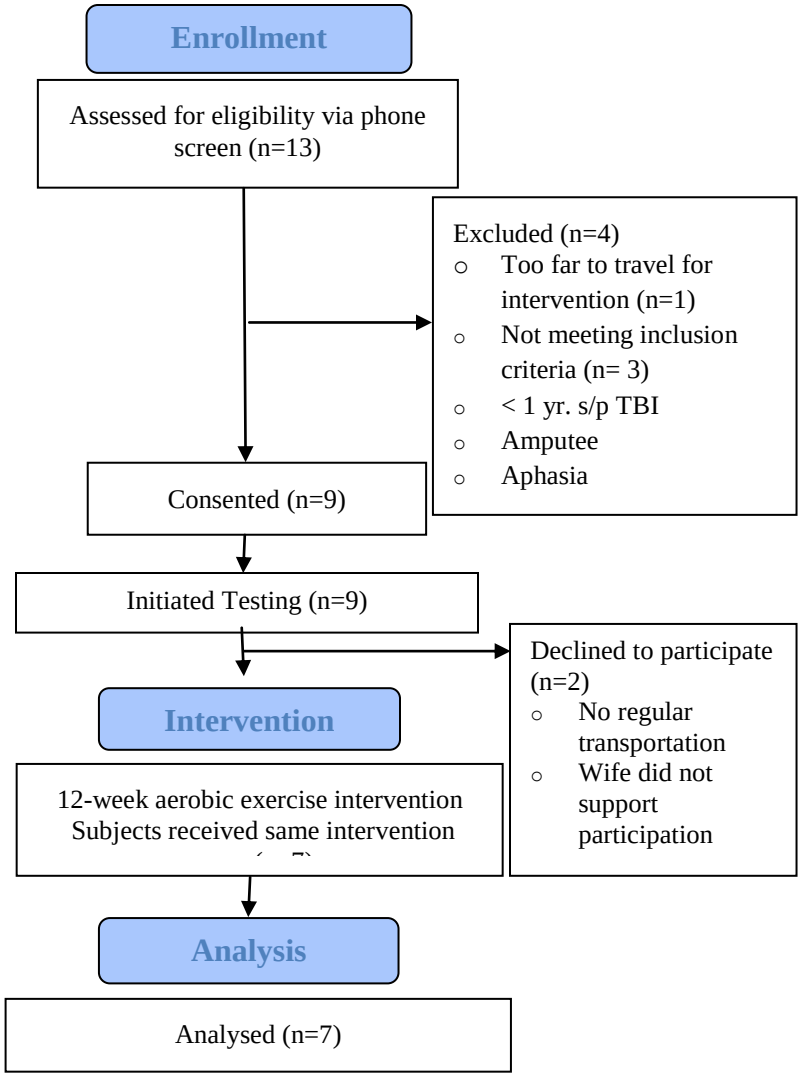

Figure 3.1. CONSORT Flow Diagram.

Subjects were community dwelling outpatients who presented sub-acute, moderate-to-severe, non-penetrating TBI and were at least one year post-injury. Injury severity was determined based on available data as follows: "moderate" if the patient had a Glasgow Coma Scale (GCS) score between 9 and 12 and loss of consciousness (LOC) between 30 minutes to 24 hours. "Severe" if the LOC was for > 24 hours and they had a Glasgow Coma Scale (GCS ≤ 8). Post-traumatic amnesia time was required to be > 1 hour. The time since injury was a mean of 11.29 years (SD ± 11.12 years, range 1-30 years). Chart reviews were completed on each subject to determine the location and etiology of their injuries as well as their LOC length. (Table 3.2 includes the demographic data for each subject).

Inclusion criteria included;

- Non-penetrating traumatic brain injury > than 1 year post injury.
- Between ages 18 and 60 years of age.
- Moderate-to-severe traumatic brain injury (TBI) evidenced by a Glasgow Coma Score of 3-12, within 72 hours of injury.[53]
- Legal competence
- Post-traumatic amnesia time of > 1 hour
- Current a Rancho Los Amigos Cognitive Scale score ≥ VII to allow for adequate participation in the cognitive testing (Appendix 2).
- Mini Mental Status Examination score > 22. (Appendix 3).
- Vision correctable to 20/40.
- Ability to ambulate >150' with or without an assistive device.

- Berg Balance Score ≥ 45 to minimize fall risk.
- >45° index finger flexion and extension to allow pushing a button
- Subjects or caregivers report of difficulties in executive functioning or memory.
- MD consent

Exclusion criteria;

- Penetrating brain injuries
- Currently participating in a regular exercise program within the last 3 months or currently enrolled in rehabilitation.
- Visual field disturbances.
- Previously diagnosed psychiatric illness as defined by DSM: Axis I Clinical Syndromes.
- Agitation
- Previously diagnosed developmental disability
- Previous myocardial infarction, cardiac pacemaker, angina, cardiac arrhythmias, aortic stenosis, pulmonary embolus, uncontrolled hypertension, acute or chronic infectious disease or uncontrolled metabolic disease
- Depression as measured by a Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 (Appendix 4). [52-54]
- Subjects could not have current substance abuse issues as determined by

the CAGE Questionnaire for Alcohol Screening and MPAI pre-existing conditions questions (Appendix 5).[54,55]

- Abnormal graded treadmill exercise test

Table 3.1. Subject demographics.

Subject	Age	Yrs. since injury	Yrs. of educ.	Type/location of TBI	GCS	Injury Severity	Etiology	RLA Score	MMSE	Berg Balance Score	PHQ-9
1	28	5.75	12	Bilateral cerebral contusions, Diffuse axonal injury	3	Severe	Motor Vehicle Accident	7	24	50	2
2	60	7	14	Left frontal subarachnoid hemorrhage	9	Moderate	Motor Vehicle Accident	9	28	52	7
3	35	1.3	12	Right frontal subdural hematoma, Diffuse axonal injury	3	Severe	Motor Vehicle Accident	7	23	48	5
4	32	11	14	Right frontal subdural hematoma	3	Severe	6 ft. fall	9	30	56	2
5	51	30	13	Bilateral cerebral contusions, Diffuse axonal injury	10	Moderate	Motor Vehicle Accident	10	30	56	0
6	59	1	14	Right frontal & parietal subarachnoid hemorrhage	3	Severe	Assault	9	27	52	5
7	46	23	16	Left temporal subdural hematoma	3	Severe	Softball to head	7	29	46	7

GCS = Glasgow Coma Scale score < 72 hours post injury(max 15), RLA = Rancho Los Amigo Scale of Cognitive Functioning level (max 10), MMSE = Mini Mental Status Exam score (max 30), Berg Balance Score (max 56, PHQ-9 = Patient Health Questionnaire-9 (max 27, > 15 indicates depression).

Table 3.2. Subject, substance use, living and work situations.

Subject	Substance Use as determined by CAGE Questionnaire and MPAI pre-existing conditions	Living Situation	Work
1	Previous ETOH abuse. Has not used since injury.	Lives with parent	Sheltered workshop
2	Previous ETOH dependence. Has not used ETOH in 34 yrs.	Lives independently	Retired
3	Previous ETOH abuse. Has not used since injury	Assisted living	Not employed
4	Previous drug/ETOH abuse. Has not used since injury	Lives independently	Paid employment
5	Previous cannabis/ETOH abuse. Has not used ETOH since 1990. Currently not using cannabis	Lives independently	Paid employment
6	Previous drug/ETOH abuse, has not used since injury	Lives with significant other	VA work program
7	Never used drugs or ETOH.	Home health assistance	Volunteer work

ETOH = alcohol. MPAI = Mayo Portland Adaptability Inventory.

3.2.3 Outcome Measures

Measures were assessed at baseline and after 12-weeks of participation in the aerobic exercise intervention (See Table. 3.3). All cognitive outcome measures were performed by the same physical therapist at the University of Minnesota for pre-and post-assessment. The physical therapist also had access to neuropsychologist and speech/language pathologist support for interpretation. Cardiopulmonary maximal treadmill testing was performed by a trained technician at the University of Minnesota Clinical and Translational Science Institute or the Veteran's Administration Medical Center cardiac lab in Minneapolis.

Table 3.3. Schedule of subject testing.

			Intervention	Day 1 Posttest	Day 2 Posttest
• **Consent** • **PHQ-9** • **CAGE** • **MMSE**	Cognitive measures • RBMT – E • PASAT • MPAI-4 • WCST-64	• Treadmill test	**12- week Aerobic Ex.**	Cognitive measures • RBMT – E • PASAT • MPAI-4 WCST-64	Treadmill test

PHQ-9 = Patient Health Questionnaire-9, CAGE Questionnaire for Alcohol Screening, MMSE = Mini Mental Status Exam, RBMT-E = Rivermead Behavioral Memory Test – Extended, PASAT= Paced Auditory Serial Addition Test, MPAI-4 = Mayo Portland Adaptability Inventory, WCST-64 = Wisconsin Card Sorting Test-64.

Cognitive Measures

1. The Rivermead Behavioral Memory Test- Extended Version (RBMT- E) was administered verbally.[56] Studies of the RMBT-E have shown it is a valid and effective tool for predicting everyday memory impairments following TBI.[57,58] The RMBT-E has been determined to have sufficient sensitivity to detect mild memory problems (t=4.87, *p=<.0001)* and to be free of ceiling and floor effects.[59] The RBMT-E was also not significantly associated with intellectual ability.[56,59]

The RBMT-E is comprised of tasks analogous to everyday situations that are problematic for people with impairments following TBI. Subtests include: First and Second Names, Belongings, Appointments, Picture Recognition (presentation), Story (immediate), Picture Recognition (identifying targets from distractors), Face Recognition (presentation), Route and Messages (immediate), Face Recognition (identifying targets from distractors), Orientation and Date, Appointments (delayed), Story (delayed), Route and Messages (delayed), First and Second Names (delayed), and Belongings (delayed).[56,59] Raw scores from each subtest are converted to standardized profile scores which range from 1-4 (since the subtests have different minimum and maximum scores. To avoid a learning effect, different versions of the RMBT-E were given to subjects at pretest (version A) and posttest (version B). Reliability for this test has been determined to be good with a Cronbach's α = .84 and an intra-class correlation (ICC) for test-retest reliability has been found to be high at.94 (*P<.001).*[57, 59] Parallel-form reliability of the RMBT has been found in the literature with correlations being .84 and .80 for forms A and B respectively. (*p<.001).*[56]

2. The Wisconsin Card Sorting Test (WCST-64, Computer Version 2 Research edition) was administered to measure prefrontal dependent executive function.[60] The WCST-64 is a shortened version of the WCST and measures changes in abstract thinking, perseveration, strategic planning, organized searching, and use of environmental feedback to shift cognitive sets, goal direction, and modulation of impulses.[61] The WCST-64 was administered by computer and required subjects to sort cards on the basis of three sorting rules: color (i.e. red, yellow, green, blue), number (i.e. 1, 2, 3, 4) or shape

(i.e. triangle, circle, star, cross). The task requires subjects to find the correct sorting rule by trial and error and computer feedback which is administered visually at the bottom of the screen and verbally of either "Correct" or "Incorrect" after each response. Once the subject chooses the correct rule, the subject must maintain this sorting rule (or set) across changing stimulus conditions while ignoring irrelevant stimuli. After ten consecutive correct matches, the sorting principle changes demanding a flexible shift in set. The standard instructions for the computerized version require the subject to respond by pressing one of four keys on the computer keyboard, each corresponding to one of the four target cards. The test is not timed and subjects were informed of this during instructions.

The WCST-64 yields a number of interrelated dependent variables.[62] Seven of these variables were analyzed: (1) total number correct (TC); (2) total number of errors (TE); (3) number of perseverative errors (PE) (consecutive responses to the same wrong sorting rule) (4) number of non-perseverative errors (NPE)(wrong responses that are not perseverative) (5) number of perseverative responses (PR)(perseverative errors plus responses that are perseverative and correct) (6) conceptual level responses (CLR)(correct matches despite coincidental runs during which more than one rule seems to apply) and (7) number categories completed (CC)(number of correct runs of ten sorts). The term "perseveration" refers to the repetition of a previous response or the inability to change responses with a new stimulus which is common following TBI or frontal lobe injury.

To successfully perform on the WCST, a subject must identify characteristics of currently displayed cards, maintain the correct response, avoid the tendency to use an incorrect sorting method until the demand changes, and inhibit the inappropriate response when it is no longer required. Factor analysis of the WCST has demonstrated three primary components to WCST performance in both normal and clinical samples: (1) cognitive flexibility and accuracy; (2) problem solving and learning; (3) response maintenance and distractibility.[93, 94] Factor 1 abilities are represented by total errors (TE), perseverative responses (PR), and conceptual level responses (CLR). Factor 2 abilities are represented primarily by non-perseverative errors (NPE) and to a lesser extent trials to complete first category (T1C). Factor 3 abilities were represented by failures to maintain set (FMS). No norms are provided for TC. For TE, PR, PE, NPE and CLR, age, education-corrected standard scores, t-scores, and percentile rankings are provided for adults. Similar scores are provided based upon the United States Census age-matched adult sample. Percentile ranks are provided for CC.

The WCST-64 has also been used as a means of classifying brain injured and control groups utilizing a logistic regression. The overall correct classification rate was 69.6%, with 65.47% of the patients and 73.54% of the control group classified correctly suggesting moderate sensitivity and specificity.[63] The WCST-64 has also been validated in adults with acquired brain damage using a Mann-Whitney U Test between matched patients and controls.[60] The patients performed significantly more poorly on each score ($p < .001$).[60] Raw scores were used for the data analysis due to questionable validity of the use of the WCST standardized scores for the computerized version of the shortened

WCST-64. Standardized scores were originally obtained from the manual and longer version of the test.[64] In clinical practice, repeat administrations of the WCST are common as a way of assessing recovery of executive function. Since the WCST-64 was given prior to and following completion of the intervention, it becomes necessary to establish test-retest reliability of the tool through the literature. Generalizability coefficients for the WCST-64 scores were analyzed by repeated measures ANOVA and averaged .74, suggesting very good overall reliability of the test.[65] The test-retest reliability was measured though a Spearman correlation with a mean of .64 for all subtests and did not reflect a learning or practice effect.[65]

3. The Paced Auditory Serial Addition Test (PASAT) was administered verbally via CD ROM as a measure of divided attention, speed of processing, working memory, and mental flexibility[66,67] Administration of the PASAT involves presenting a series of single digit numbers where the two most recent digits must be summed. For example, if the digits '3', '6', and '2' were presented, the participant would respond with the correct sums, which are '9' and then '8'. The participant must respond prior to the presentation of the next digit for a response to be scored as correct. Each full test trial consisted of 60 digits (numbers 1-9 in random order). Two rates of the PASAT were administered, numbers stated every 3 seconds (slow speed) and numbers stated every 2 seconds (fast speed).

A significant practice effect has been identified with the PASAT between the first and second administration of the test in both normal subjects and TBI regardless of the time

interval between testing. Baird et al. (2004) reported comparable increases in performance after groups had experienced either a 20-min, 1-week or 3-month test–retest interval.[68] Practice effects on memory tests often occur when the information to be learned (e.g., word list) is the same at test and retest. However, it is unlikely that this approach can be used to explain practice effects that occur with the PASAT. The current explanation for practice effects seen in the PASAT is that it is a difficult and complex test. Due to this complexity, subjects require time and practice to develop an effective strategy to perform the test. Effective strategies are probably not fully developed until after an initial administration has been completed, then it becomes general procedural knowledge that is retained for subsequent administrations. Subjects were given a practice test for each speed prior to the actual pretest and posttest to allow for a strategy to develop, thereby reducing the practice effect. To further avoid a practice or learning effect, different versions of both speeds of the PASAT were given to subjects at pretest (version A) and posttest (version B) approximately 3 months apart. Normative data on the PASAT has been reported on 101 healthy adults with r >.90 test- retest reliability. [66] The scores reported for the PASAT are the number of correct responses for each trial (maximum = 60) and the percentage of correct answers.

4. The Mayo-Portland Adaptability Inventory (4th edition) (MPAI-4) was administered verbally by the investigator to the TBI subject as a means of assessing the subjects perception of their disability before and following the 12-week exercise intervention.[55,69-72] The MPAI-4 test total score reflects overall disability, as well as three subscale scores for the Ability Index (range 0-47), Adjustment Index (range 0-46), and Participation

Index (range 0-30). Item reliability of this test has been excellent (r=.99), with good person reliability (r=.78) between individuals with brain injury, significant others and staff. The MPAI-4 has also demonstrated good inter-rater reliability (r= .88), and adequate to excellent test-retest reliability (Spearman rho = .45-.93 all correlations significant, $P < .001$.[71]

The Ability Index is composed of 13 items to assess mobility: use of hands, vision, audition, dizziness, motor speech, verbal communications, nonverbal communication, attention/concentration, memory, fund of information, novel problem solving, and visuospatial abilities. The Adjustment Index is composed of 12 items: anxiety, depression, irritability/ anger/ aggression, pain and headache, fatigue sensitivity to mild symptoms, family relationships, initiation, social contact, and leisure and recreational activities. The Participation Index is composed of 8 items: initiation, social contact, leisure, self-care, independent living, employment, transportation, and money management. Each item is rated on a 5-Likert rating scale: 0, no problem; 1, mild problem but does not interfere with activities; 2, mild problem that interferes with activities up to 24% of the time; 3, moderate problem that interferes with activities 25-75% of the time; and 4, severe problem that interferes with activities greater than 75% of the time.

Following scoring of the MPAI-4, raw scores were converted to T-scores referenced to a national data sample. The T-scores have a mean of 50 and a standard deviation of 10 with reference to the sample on which it is based. T scores range from (-38 to 106 for the

total MPAI-4 score, -4 to 109 for the Ability subscale, -6 to 94 for the Adjustment subscale, and 7 to 74 for the Participation Scale. The predictive validity of the MPAI-4 has been demonstrated in many studies. Staff administered MPAI has been determined to be the best predictor of long term vocational and independent living outcome following rehabilitation for persons with TBI. Logistic regression analysis included age, education, severity of injury, time since injury, and Rasch-converted MPAI scores as potential predictors. Analysis showed that MPAI alone predicted vocational status one year after rehabilitation (correct classification 67%, χ^2= 5.33, p<.05). Logistic regression of the same set of variables also found the MPAI was the only significant predictor of independent living status one year after rehabilitation (correct classification 70%, χ^2 = 6.85, p<.01). [55,73] The MPAI-4 has also been found to be sensitive to change in studies of rehabilitation interventions.[18]

Aerobic Capacity

To determine each subject's cardiorespiratory fitness and intervention exercise intensity, a modified Balke-Ware treadmill test protocol was performed.[74] During the test, subjects wore a non-rebreathing mask and nose plugs while a metabolic cart was used to collect expired gases. Subjects also wore a blood pressure cuff and a 12-lead electrocardiogram (ECG) to monitor blood pressure, heart rate, and rhythm. After becoming familiarized with the treadmill, subjects walked at 3.3 mph at 0% grade for three minutes with the grade then increasing by 2.5% every two minutes. Subjects were closely guarded and allowed to use the handrail to minimize risk of falling. Maximal effort was identified by the following criteria: a respiratory exchange ratio (RER) of 1.15

or more, a failure to increase heart rate with increases in exercise intensity, a plateau in VO_2, +/- 10 beats/minute (bpm) above age predicted maximum heart rate, or subject fatigue.[75]

This modification of the original Balke-Ware protocol has been previously used in persons with TBI.[76] Cardiovascular stability was measured continuously through changes in heart rate and rhythm via a 12-lead ECG. Participants were also monitored every minute with Borg's Rating of Perceived Exertion Scale to assess the subject's perceived effort.[77-79] VO_2 (oxygen consumption) was measured every 15 seconds via a non-rebreathing mask. Gas and treadmill calibrations were performed on the equipment prior to each test.

American College of Sports Medicine guidelines were used to determine whether the testing should terminate prior to completion of the test.[75] These criteria included ST depression more than 2 mm, increased nervous system symptoms, sustained ventricular tachycardia, chest discomfort, and +/- 10 beats over age predicted maximal heart rate. The peak heart rate, exercise duration, peak aerobic capacity (VO_2 max) and respiratory exchange ratio (RER) were monitored and recorded during the exercise test. VO_2 max refers to the maximum amount of oxygen that an individual can utilize during intense or maximal exercise. It is measured as milliliters of oxygen used in one minute per kilogram of body weight.[75] VO_2 max has been shown to be the most accurate measurement of functional capacity and is an indicator of overall cardiopulmonary health.[80]

Intervention

An aerobic exercise intervention based on principles for exercise prescription according to the American College of Sports Medicine was conducted at the Minneapolis VA Medical Center Fitness Center or Bethesda Rehabilitation Hospital Physical Therapy clinic in St. Paul, MN.[75]The aerobic exercise intervention occurred in a group format led by trained Doctor of Physical Therapy (DPT) students who were supervised by a licensed Physical Therapist. Each subject participated in the aerobic exercise intervention for 45-60 minutes 3 times a week for 12-weeks. Attendance and compliance were logged during each visit (Table 3.6).

Exercise duration, intensity, and heart rate were also logged prior to, during and following the aerobic exercise period for each subject visit. Monitoring of subjects ensured that they were within the proposed intervention parameters. Subjects had the choice of performing their program on an elliptical trainer, treadmill, cycle ergometer, or upper extremity ergometer as long as they were able to obtain their designated target heart rate for that week. The maximal heart rate (max HR) for each subject was determined through the equation (220 –age) and the target heart rate listed in the Aerobic Exercise Protocol below. The 1 hour session included a 5-10 minute warm-up at 20-30% of the subject's max HR, an aerobic period of 20-40 minutes, and a 5-10 minute cool down period ramping down to 20-30% of max HR. The intensity of the aerobic period for each exercise session was determined by the following percentages:

Aerobic Exercise Protocol

Week 1-3: Aerobic exercise will be at a light level for 15-20 minutes at 40-50% of

maximal heart rate.

Week 4-7: Aerobic exercise will be at a moderate level for 20-30 minutes at 50-60% of maximal heart rate.

Week 8-12 Aerobic exercise will be at a high intensity level for 20-30 minutes at 60-80% of maximal heart rate.

Subjects were allowed to progress at a faster rate than the one prescribed above if cardiovascular measures indicated that it was safe to do so.

Data Analysis

Analysis was performed using software from SAS Institute Inc. (SAS/STAT ®9.2, Cary, NC: SAS Institute Inc. 2009). An examination of normality revealed that the aerobic capacity and cognitive data were skewed and not normally distributed based on the Kolmogorov-Smirnov test Accordingly, a nonparametric Wilcoxon Signed-Ranks test was utilized to address the research hypotheses related to cognition. The Wilcoxon Signed-Ranks test was utilized to evaluate the differences between the change in the pretest/ posttest data for the RMBT-E, PASAT, WCST-64 and MPAI-4. The non-parametric Wilcoxon Signed-Ranks test is analogous to the parametric paired t-test and can be appropriately used to conduct a comparison of two related samples or repeated measurements when the dependent variable is not normally distributed or if the data are nominal or ordinal. The Wilcoxon Signed-Ranks test is designed to test the direction and magnitude of the difference between two population mean ranks.[81] And it is often used for matched pairs for pretest/posttest intervention data. Significance was set at an alpha level of $P < .05$ for each analysis. A correction for multiple comparisons was not used

since it was felt to be overconservative and inflexible a restriction for this small study. [82]

3.3 Results

3.3.1 Aerobic Capacity Results

Hypothesis 1. (A.3) required a comparison of the change in the TBI subjects' pre-exercise and post-exercise VO_2 max during a graded treadmill test to measure the maximal oxygen uptake. The ratio scale data for this test were not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Wilcoxon Sign-Ranks test results indicated that following participation in 12-weeks of aerobic exercise, there was a significant improvement in the subjects' VO_2 max (Z= 14), Mdn (-3.6), (IQR = 4.1), (P = .016). All seven subjects demonstrated improved cardiovascular fitness following participation in the 12-week aerobic exercise program with a mean improvement of 4.2 ml/kg/min (see Figure 3.2). No adverse events were reported during the maximal treadmill testing nor during any of the training sessions. Subject compliance with the exercise intervention is shown in Table 3.4. Mean compliance was 84%. It is also important to distinguish that Subject 4 and 5 had markedly decreased compliance compared to their counterparts (42 an 64% respectively).

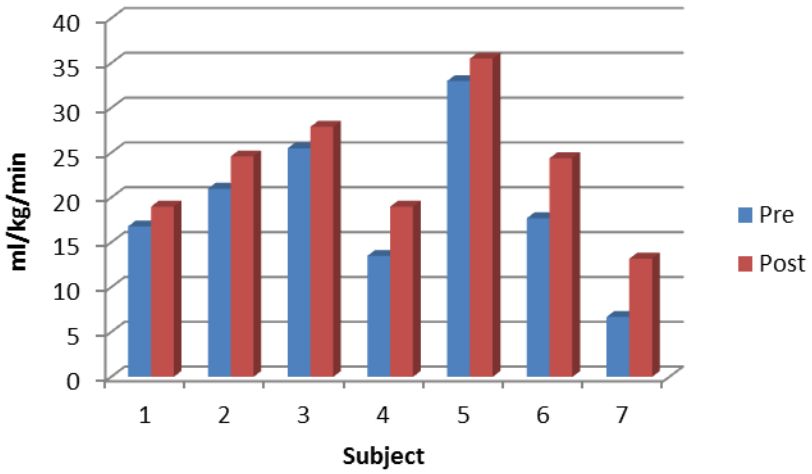

Figure 3.2. Individual subject's improvement in aerobic capacity following the aerobic exercise intervention.

Table 3.4. Intervention compliance.

Subject	Number of visits	% Compliance	Exercise device
1	36	100%	Treadmill & Bike
2	36	100%	Treadmill
3	35	97%	Treadmill
4	15	42%	Bike
5	23	64%	Treadmill
6	32	89%	Treadmill & Elliptical
7	35	97%	Bike

3.3.2 Cognitive Results

Rivermead Behavioral Memory Test-Extended

Hypothesis $1._{A.1)}$ called for a comparison of the change in the TBI subject's pre-exercise and post-exercise total and subscale scores on the RBMT-E to measure changes in everyday memory. The RBMT-E includes ten subtests to measure specific aspects of memory. Raw scores from each subtest were converted to standardized profile scores since the subtests each have different minimum and maximum scores. The profile scores

are recorded as interval data. The data for this test were not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Pretest and posttest difference scores were then used for statistical analysis. Following participation in 12-weeks of aerobic exercise, the group results did not demonstrate a significant change in any of the individual subtests. However, the Wilcoxon Sign-Ranks test results did demonstrate that the RBMT-E total profile score showed significant improvement in everyday memory following participation in the 12 aerobic exercise intervention. Statistics for the RBMT-E are shown in Table 3.5 below.

Table 3.5. Standardized Rivermead Behavioral Memory Test - Extended (RBMT-E) statistics.

Subtest	Mdn	IQR	Wilcoxon Sign Rank Test Statistic	P Value
First Names	0.00	1.00	-1.50	0.75
Second Names	1.00	4.00	0.00	1.00
Belongings & Appointments	2.00	4.00	7.50	0.16
Picture Recognition	1.00	2.00	3.50	0.44
Story (immediate)	0.00	2.00	2.50	0.75
Story (delayed)	0.00	1.00	-3.00	0.25
Face Recognition	1.00	2.00	2.50	0.78
Route (immediate)	2.00	3.00	5.00	0.13
Route (delayed)	0.00	2.00	2.50	0.50
Messages (immediate)	0.00	1.00	1.50	0.50
Messages (delayed)	1.00	2.00	5.00	0.13
Orientation & Date	0.00	1.00	3.00	0.25
***Total Profile Score**	5.00	4.00	14.00	0.02

(Mdn) Median, (IQR) interquartile range

Individual analysis revealed that all seven of the subjects improved their everyday memory as demonstrated by changes in the total RMBT-E following the exercise intervention with a mean change of six standardized points (Figure 3.3.)

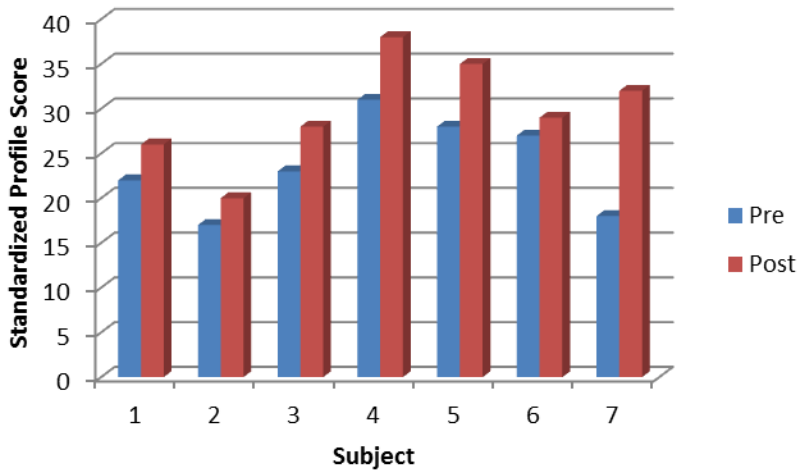

Figure 3.3. Comparison of the Total Standardized Profile Score of the RBMT-E for each individual subject.

After identifying subtle changes in memory in the TBI population, the RBMT-E is further able to classify profile scores into subgroups of abilities.[59] Designated ratings and cut-off points of the RBMT-E as a measure of everyday memory have been identified as: Exceptionally Good (43-48) Good (37-42), Average (28-36), Poor (19-27), Impaired (0-18).[59] Subjects' memory ratings based on their scores are listed in Table 3.6. All seven subjects did demonstrate improved scores on the total RBMT-E profile scores (mean change of 6 points) following participation in 12-weeks of aerobic exercise. Five of the subjects also improved their rating of everyday memory functioning with four of the subjects progressing to either the average or good category following 12-weeks of aerobic exercise. One subject was already at the average level prior to aerobic exercise

and maintained the average rating following the aerobic exercise despite improving their total score.

Table 3.6. RBMT-E scores and ratings comparison prior to and following the exercise intervention.

Subject	Pre-exercise Total Profile Score	Pre-exercise Rating	Post-exercise Total Profile Score	Post-exercise Rating
1	22	Poor	26	Poor
2	17	Impaired	20	Poor
3	23	Poor	28	Average
4	31	Average	38	Good
5	28	Average	35	Average
6	27	Poor	29	Average
7	18	Impaired	32	Average

Exceptionally Good (43-48) Good (37-42), Average (28-36), Poor (19-27), Impaired (0-18).

Paced Auditory Serial Addition Test

Hypothesis 2. $_{(A.1)}$ called for a comparison of the change in TBI subjects' pre-exercise and post-exercise PASAT scores for both the three second (slow) and two second (fast) rates to measure working memory. The ratio data for this test was not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Pretest and posttest difference scores were then used for statistical analysis. Wilcoxon Sign-Ranks test results indicated that following participation in 12-weeks of aerobic exercise, there was a significant improvement in the PASAT scores at the 3 second (slow) speed and the 2 second (fast) speed (Table 3.7).

Table 3.7. Paced Auditory Serial Addition Test (PASAT) statistics.

Timing	Mdn	IQR	Wilcoxon Sign Rank Test Statistic	P Value
Slow speed	8.00	4.00	14	.02
Fast speed	5.00	5.00	13	.03

(Mdn) Median, (IQR) interquartile range.

All seven subjects also all demonstrated improvement in their working memory as demonstrated by improvements in their accuracy on the PASAT during the slow speed following the exercise intervention with a mean change of seven points (Figure 3.4). And six out of the seven improved their accuracy on the PASAT during the faster speed with a mean change of eight points (Figure 3.5).

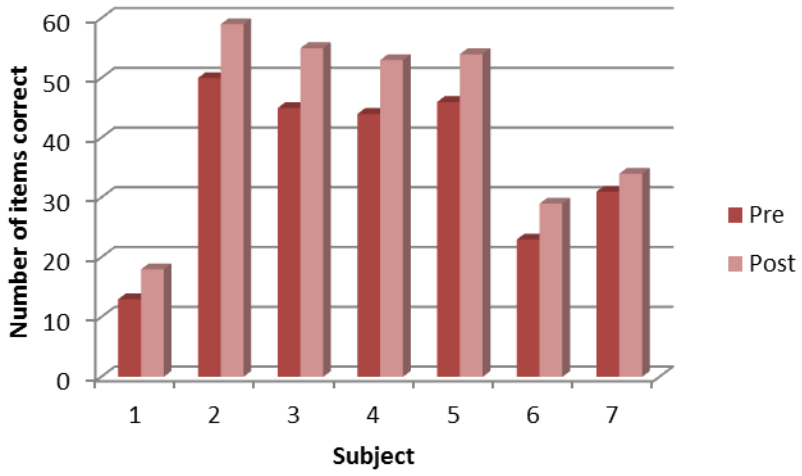

Figure 3.4. Comparison of the number correct for all subjects' during the slower speed of the Paced Auditory Serial Addition Test pre and post aerobic exercise intervention.

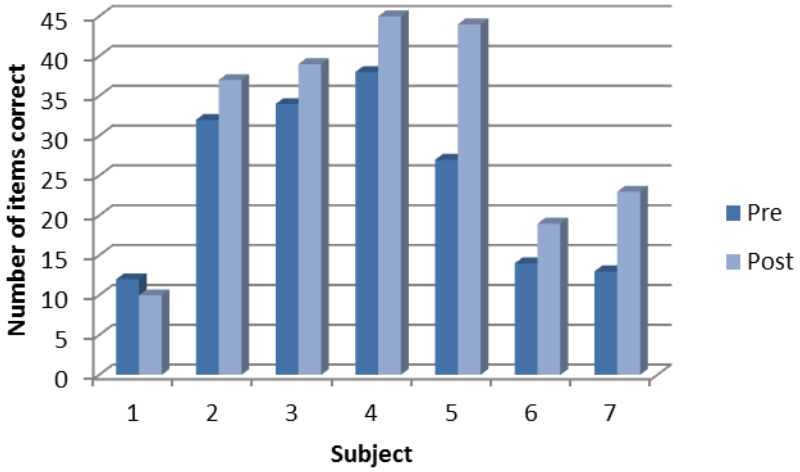

Figure 3.5. Comparison of the number correct for all subjects' during the faster speed of the Paced Auditory Serial Addition Test pre and post aerobic exercise intervention.

Wisconsin Card Sorting Test-64

Hypothesis 3.$_{(A.1)}$ necessitated the comparison of TBI subjects' pre-exercise and post-exercise performance on the WCST-64 to measure changes in executive function. Raw scores were used for analysis due to questionable validity of the use of the WCST standardized scores for the computerized version of the shortened WCST-64.[61] Seven indexes change scores were analyzed: (1) total number correct (TC); (2) total number of errors (TE); (3) number of perseverative errors (PE); (4) number of non-perseverative errors (NPE); (5) number of perseverative responses (PR); (6) conceptual level responses (CLR; (7) number categories completed (CC). The interval data for this test were not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Pretest and posttest difference scores were then used for statistical analysis. Wilcoxon Sign-Ranks test results indicated that following participation in 12-weeks of aerobic exercise, there was not a significant difference in the WCST-64 as a measure of executive function. Test statistics are noted below in Table 3.8.

Table 3.8. Wisconsin Card Sorting Test (WCST-64) statistics.

Variable	Mdn	IQR	Wilcoxon Sign Rank Test Statistic	P Value
TC	5.00	17.00	11.00	0.08
TE	-5.00	17.00	-11.00	0.08
PE	-3.00	8.00	-10.00	0.11
NPE	-4.00	7.00	-8.50	0.09
PR	-5.00	11.00	-10.50	0.09
CLR	11.00	32.00	11.00	0.08
CC	1.00	2.00	8.50	0.13

(TC) total number correct,(TE) total number of errors, (PE) number of perseverative errors, (NPE) number of non-perseverative errors, (PR) number of perseverative responses, (CLR) conceptual level responses, (CC) number categories completed (Mdn) Median, (IQR) interquartile range

During individual subject observation, however, it should be noted that five out of the seven subjects did demonstrate improvement in the total number of correct items answered with a mean change of 13 items (Figure 3.6). Of note, one of the subjects (Subject 4) that did not improve, demonstrated questionable effort during this WCST posttest which may have impacted the results.

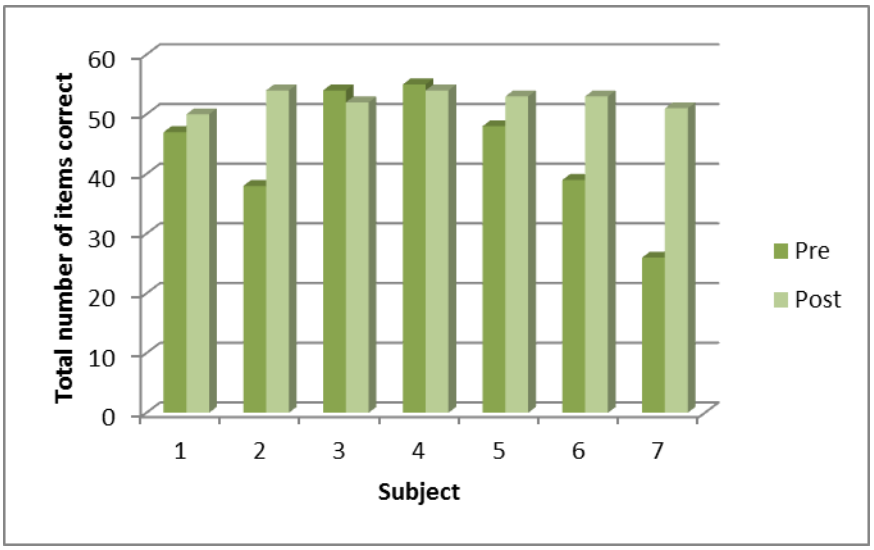

Figure 3.6. Comparison of the number correct (raw scores) for all subjects' during the WCST pre and post aerobic exercise intervention.

Mayo Portland Adaptability Inventory-4

Hypothesis $1._{(A.2)}$ called for a comparison of TBI subjects' pre-exercise and post-exercise three subscale change scores (Ability Index, Adjustment Index, and Participation Index)and the total score on the MPAI-4 to measure the subjects' disability and global outcome. Raw scores were standardized to T-scores referenced to a national data sample for the analysis. The data for this test of disability were not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Pretest and posttest difference scores were then used for statistical analysis (Table 3.11). Wilcoxon Sign–Ranks test results indicated significant improvement in the group's overall total standardized MPAI-4 change scores following participation in the 12-weeks of aerobic exercise. It was also observed that all seven of the subjects improved in their overall standardized score following the exercise intervention (Figure 3.9). Overall scores range from of 0–111, with lower scores indicating greater community integration. Unfortunately, no studies establishing minimum clinically important differences (MCIDs) are available for the MPAI thereby limiting the interpretation of the results

Table 3.9. Standardized Mayo-Portland Adaptability Inventory (MPAI-4) statistics

Subscale	Mdn	IQR	Wilcoxon Sign Rank Test Statistic	P Value
Abilities	-8.00	10.00	-14.00	.02
Adjustment	-11.00	17.00	-14.00	.02
Participation	-7.00	14.00	-9.50	.13
Total	-11.00	17.00	-14.00	.02

(Mdn) Median, (IQR) interquartile range

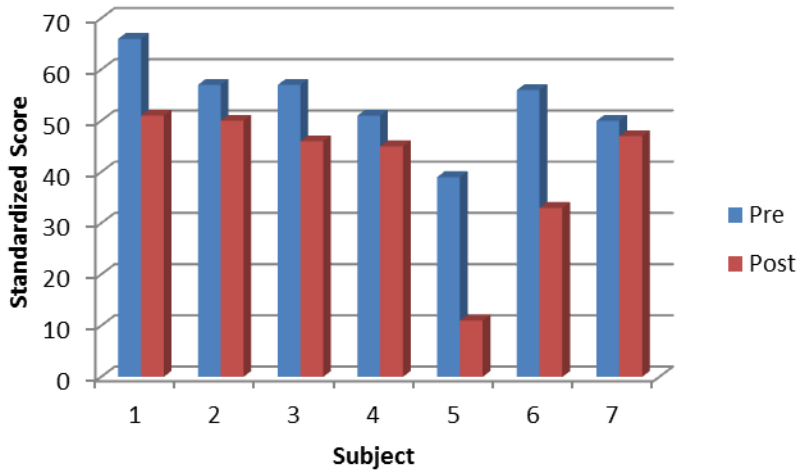

Figure 3.7. Comparison of all subjects' MPAI-4 standardized total scores pre and post aerobic exercise intervention. Lower scores indicate improvement.

For acquired brain injury, total standardized scores less than 30 indicate a good outcome. A total score between 30-40 indicates mild limitations, 40-50 indicate mild-moderate limitations, 50-60 indicate moderate –severe limitations and a score above 60 indicates severe limitations. It is important to note that six out of the seven subjects improved their rating of disability following the exercise intervention (Table 3.10).

Table 3.10. MPAI-4 total standardized scores and ratings comparison prior to and following the exercise intervention.

Subject	Pre-exercise Total Standardized Score	Pre-exercise Rating	Post-exercise Total Standardized Score	Post-exercise Rating
1	66	Severe	51	Mod-Severe
2	57	Mod-Severe	50	Mod-Severe
3	57	Mod-Severe	46	Mild-Mod
4	51	Mod-Severe	45	Mild-Mod
5	39	Mild	11	Good outcome
6	56	Mod-Severe	33	Mild
7	50	Mod-Severe	47	Mild-Mod

The standardized Ability scores and the standardized Adjustment scores also indicated significant improvement at following participation in the 12-weeks of aerobic exercise.

There were no group differences in the standardized Participation change scores following the aerobic exercise intervention. It was also noted that individually all seven of the subjects demonstrated improvement in the Abilities subscale with a mean change of 9 points on their standardized score (Figure 3.8) and the Adjustment scale with a mean change of 14 points on their standardized score Figure 3.9). But, in the individual observational analysis it observed that the total Participation score improved for only six out of the seven individual subjects with a mean change of 9 points on their standardized score (Figure 3.10). It should be noted that Subject 5 who showed no change in the Participation score had a very high level, independent level of participation compared to the other subjects at the pretest.

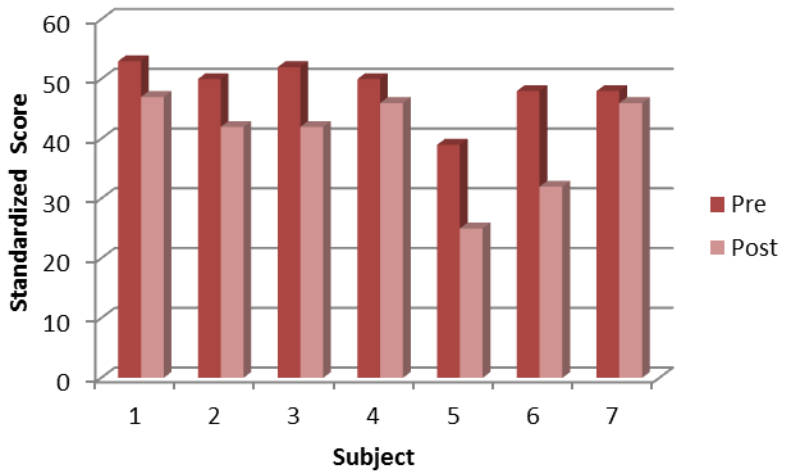

Figure 3.8. Comparison of all subjects' MPAI-4 standardized Ability scores pre and post aerobic exercise intervention. Lower scores indicate improvement.

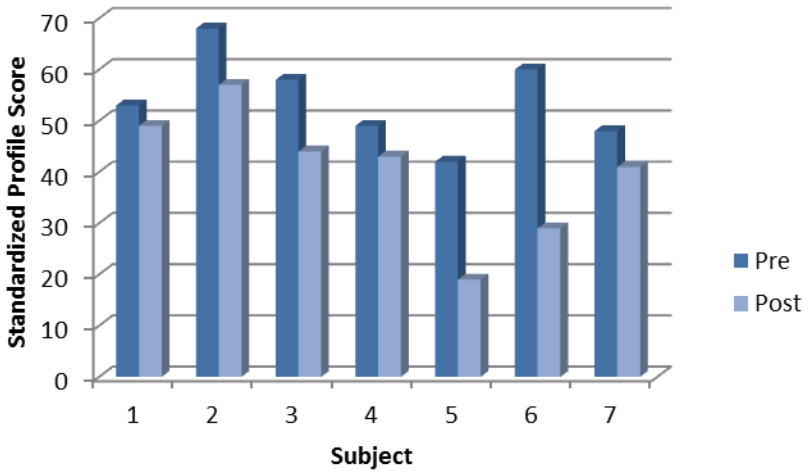

Figure 3.9. Comparison of all subjects' MPAI-4 standardized Adjustment scores pre and post aerobic exercise intervention. Lower scores indicate improvement.

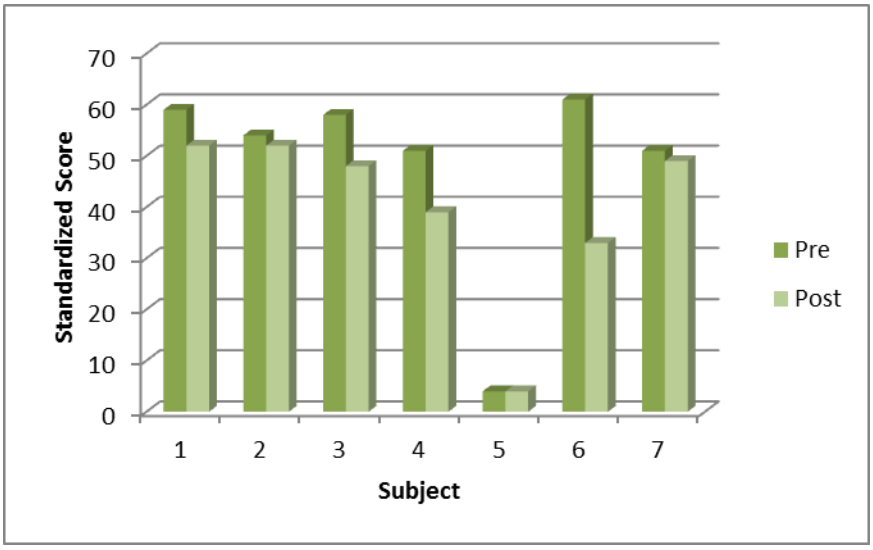

Figure 3.10. Comparison of all subjects' MPAI-4 standardized Participation scores pre and post aerobic exercise intervention. Lower scores indicate improvement.

3.4. Discussion

The aims of this preliminary clinical study were to investigate the changes in the aerobic

capacity, everyday memory, working memory, executive function and disability in a moderate-to-severe TBI population following 12-weeks of an aerobic exercise intervention using behavioral measures. To our knowledge, this study is one of the first to examine this effect in a human population following TBI. The results of this study demonstrated increased aerobic capacity, improvements in overall everyday and working memory, as well as improved aspects of some areas of perceived disability.

3.4.1 Change in Aerobic Capacity

For many different reasons, a large majority of persons with TBI adopt a sedentary lifestyle leading to reduced cardiovascular fitness. Chronic TBI patients' peak aerobic capacities have been found to be approximately 65% to 74% of neurologically intact adults of the same age.[75, 84] Many persons with TBI are young and likely to survive into older age with resultant sedentary lifestyle they have adapted. This sedentary lifestyle could lead to the development of secondary health problems that will only add to their functional impairments and potentially burden an already strained healthcare system. The baseline VO_2 measurements of the subjects in this study are comparable with those in other studies and further illustrate the poor cardiovascular fitness of people in the chronic phase of TBI. The importance of maintaining healthy cardiovascular fitness is important for both neurologically intact as well as TBI and other neurologically impaired populations. Aerobic exercise has long been associated with improved cardiovascular health and prevention of many diseases including cancer and diabetes and depression. Depression is also a common psychiatric diagnosis following TBI regardless of injury severity and is associated with poor functional outcome, cognitive deficits and reduced

quality of life.[85, 86] As hypothesized, in the group analysis, the subjects significantly improved their cardiovascular fitness as measured by the change in VO_2 max following the 12-week aerobic exercise intervention (P = .016). The results of this study agree with those that have investigated the response of other TBI subjects to aerobic exercise.[84] Regardless of the impact of aerobic exercise on cognition, the improvement of all seven subjects' cardiovascular fitness (mean improvement of 4.2 ml/kg/min) is beneficial in and of itself given their initial low initial fitness levels (Figure 3.1). These results, although not unexpected, are important for the overall health and well-being of each individual subject. It is also important to note that despite subject's memory and the inherent unreliability of the TBI population, the mean compliance during the 12-week exercise intervention was at 84% which is approximately 20-35% higher than exercise compliance averages in other impaired populations like diabetes, or CVA (50-65%). [83,84]

3.4.2 Change in Everyday Memory

Both verbal and visual memory are vulnerable to moderate-to-severe TBI. In clinical practice it is not unusual to encounter TBI patients who look and sound like they have intact cognition yet are unable to return to gainful employment and function independently in the community due to memory issues. Memory deficits affect the safety of TBI patients, making them vulnerable citizens in the home (e.g., forgetting to turn the stove off), community (e.g., forgetting directions), and work (e.g., forgetting important appointments). And while these patients do benefit from repetition, the slope for their learning is lower than that of controls making memory impairments one of the most persistent and debilitating sequelae following TBI. [87]

The RBMT-E is considered a bridge between laboratory-based measures of memory and assessments obtained by questionnaire and observation. The RBMTE-E is therefore administered and standardized like any psychological test but utilizes analogues of everyday memory that are difficult for patients with brain injury rather than using abstract experimental material. And it is considered sensitive to subtle memory changes in the TBI population.[59] In the group analysis, the RBMT-E did not show significant changes in any of the individual subtests. Surprisingly however, the total RMBT-E did show a significant change ($P<.015$) in everyday memory following participation in the 12-week aerobic exercise intervention. This finding should not be considered as unusual since even in the early validation of the RMBT-E, the total overall score was shown to be substantially more sensitive than any of the individual subtests alone.[56]

Equally as important is the gain in subject's overall categories of everyday memory abilities. Remedial treatment of everyday memory has not only been a persistent deficit following TBI, but it has also been notoriously difficult to treat. Currently, cognitive rehabilitation has centered around two approaches. The first utilizes a structured set of therapeutic activities designed to retrain an individual's memory. However, systematic reviews and meta-analyses of this approach conclude that "results for memory rehabilitation are mixed and weak". [85] The second approach uses an approach of compensation which trains TBI patients to use memory aids like electronic organizers or planners to accommodate for their impairment. This approach is indeed useful, but it does not address the possibility of promoting neurologic plasticity or improvement.

It is well established that aerobic exercise underlies many neurologic benefits which promote neuroplasticity, such as angiogenesis, neurogenesis and synaptogenesis especially in areas related to cognition.[30,40,86-92] Based on this previous literature, it appears that aerobic exercise creates an environment which is conducive for optimal rehabilitation. This study, although limited in scope, has demonstrated an improvement in the everyday memory of its subjects. Combined with previous literature regarding the underlying neurophysiological improvements found with aerobic exercise, a larger study combining aerobic exercise to first create an underlying, positive, neuronal environment with cognitive rehabilitation to retrain memory may be the next step in pushing ahead TBI memory rehabilitation.

3.4.3 Change in Working Memory

As previously mentioned, working memory has been shown to be an area of cognition particularly vulnerable to TBI. Research has shown that working memory is a unique system that operating via a dynamic interaction between memory and executive function and is the driving force needed for learning. Research related to working memory has also shown practical implications. Working memory forces people to actively maintain information until they engage in the processing component of the task, as well as inhibit a pre-potent response. Response inhibition is a hallmark of the central executive aspect of working memory.

The Paced Auditory Serial Addition Test (PASAT) is a frequently used and established measure of working memory and has been applied to examine the cognitive sequelae of

TBI.[65.66] The interaction between working memory and executive function is especially useful for predicting how well people can reason and adapt to increasingly complex environments. Gronwall and Writson (1981), tested 10 patients with mild TBI. These patients were unable to return to work because of poor concentration, fatigue, irritability and headaches and their PASAT scores were consistently lower than those obtained by normal controls.[93] Repeated testing resulted in PASAT scores returning to normal with concomitant decrease in their symptoms. Stuss et al., (1989) reported that PASAT scores for severe TBI patients with persistent complaints were significantly lower at each rate than for controls when tested 2-144 months post injury.[94] Thus, overall the PASAT has been repeatedly shown to have a high degree of sensitivity in symptomatic patients following TBI.

In TBI subjects, the PASAT has also been reported through fMRI and SPECT to activate the frontal and parietal cortices which have been implicated as the brain network associated with working memory.[88, 89] Compared to neurologically intact adults, TBI subjects have been found to have a different pattern of activation during the PASAT. TBI subjects generally demonstrate increased activation in the prefrontal cortex and a more distributed locus of activity compared to controls suggesting a less efficient compensatory pattern.[88, 89]

Within the context of this study, significant changes were found for the group analysis in both the slow speed ($P = .016$) and the fast speed ($P = .031$) demonstrating improved working memory and speed of processing following the 12-week aerobic exercise

intervention.

The findings in this study are consistent with the literature. In a recent meta-analysis of the acute effects of exercise on working memory in neurologically intact adults a significant beneficial effect was noted.[90] Several other studies have also observed improvements on the Stroop and the PASAT working memory tasks after an acute episode of aerobic exercise.[91, 92] Specifically, Lichtman and Poser observed improved and selective performance in working memory immediately after exercise relative to a control condition and more particularly on the subject's ability to inhibit a pre-potent response.[91] Further support for the beneficial effects of acute exercise on inhibitory control has been shown by Tomporowski et al., who observed improved performance on a PASAT after a 30-min recovery period after exercise.[92] In this preliminary study of a longer period of exercise (12-weeks) in a neurologically damaged TBI population, we observed a similar improvement in working memory. Taken together, the literature and the results of this study suggest that exercise may appear to positively impact working memory with the next step being to investigate the underlying mechanisms by which these improvements are occurring.

3.4.4 Change in Executive Function

Executive function is another domain of cognition that is often impaired following TBI. Executive function incorporates the complex sub-categories of planning, reasoning, set-shifting and monitoring with the constantly updating working memory system. Executive functions are highly applicable to functional independence. People need

executive functioning skills to keep themselves and their possessions organized, maintain appointments, meet deadlines, distinguish appropriate behavior from inappropriate behavior, learn from mistakes and incorporate new information in a seamless and productive way. More so than speed of processing and memory, executive function has been found to be strongly related to functional outcome following TBI.[6] This finding suggests individuals might be able to compensate for slowed processing and memory difficulties following TBI by using compensatory strategies. But to do so, TBI subjects will need the executive function skills in order to successfully integrate into community living.[6]

The Wisconsin Card Sorting Test (WCST) is a widely used neuropsychological assessment for measuring executive function, especially in the TBI population. The WCST is considered to be particularly sensitive to the effects of frontal-lobe injury and thus serves as an important indicator of executive dysfunction in patients with TBI.[61] Within the context of this study, the group analysis showed no significance on any of the sub-categories of the WCST-64 following 12-weeks of aerobic exercise. The confirmation of the null hypothesis is surprising since executive function has historically been linked to aerobic exercise. However, upon further review, literature appears to support only a relationship between elevated executive function and those adults who have overall better fitness. It does not necessarily support the use of aerobic exercise as an intervention to improve existing executive function. In a study investigating the relationship between physical activity levels and executive function abilities, young adults who were more physically active performed better than their sedentary

counterparts.[95] Studies have also shown that subjects that are more aerobically fit, have a larger volume of the dorsal lateral prefrontal cortex (DLPFC) which is involved in executive function.[96] However, in studies looking at the effect of acute exercise on executive function, there does not seem to be an immediate improvement in executive function, unlike studies of working memory. [97,98] In regards to the subjects in this study, it is possible that since they did not reach a level of aerobic capacity that was normal for their age, they did not reach a yet to be determined threshold required for improving executive function.

It is also possible that the use of the measurement tool of the WCST-64 itself was not a sensitive enough measure to determine executive function changes following this intervention. In an analysis of the WCST-64, group comparisons have been found to be particularly difficult for the individual variables since the large variability seen in WCST performance can overwhelm the low sensitivity of the measures. [93] This limited sensitivity of the measure – coupled with the small sample size, and need for use of nonparametric statistics as well as the possibility that executive function may not exhibit as robust of change may be issues to consider when reviewing the group findings from the WCST-64 in this preliminary study.

3.4.5 Change in Disability

TBI has been the leading cause of long-term disability and major contributor to increasing health costs in the United States, even before factoring in the current military conflicts. The most common and persistent impairments following TBI tend to be

cognitive impairments which limit individuals from re-entering the community and pursuing their educational and occupational goals, thereby limiting patient's overall productivity.

The Mayo-Portland Adaptability Inventory (MPAI-4) is a measure global brain injury outcome and perceived disability that is increasingly used to evaluate TBI patients and outcomes in many brain injury programs throughout the U.S. It includes three sub-categories of Abilities, Adjustment and Participation. Each of these categories respectively represent the physical, cognitive and emotional issues commonly affected by TBI patients in many stages of recovery.[68] Evaluation of the three subscales of the MPAI-4 have shown moderate correlation with each other and represent progressively more difficult regions of global outcome following TBI.[68] In the factor analysis, disabilities noted on the Abilities scale was most strongly correlated with the most severe global impairment, followed by the Adjustment scale and then the Participation scale.

Following the 12-week aerobic exercise intervention, group analysis demonstrated significant improvement in the overall total MPAI-4 standardized scores ($P = .016$). It was also observed that all seven of the subjects improved in their overall standardized score following the exercise intervention (Table 3.15). It is interesting to note that the two patients who were not as compliant as the others (Subjects 4 and 5), also showed changes in most categories. This finding again demonstrates that the dosage of exercise occurring three times per week for twelve weeks may not be an essential factor in the overall improvement of the subjects. It is also important to observe that since a retention

test was not done, it is difficult to infer how long the cognitive improvements following the intervention might last.

Following the 12-week aerobic exercise intervention, group analysis demonstrated significant improvement in the Abilities (*P =.013*) subscale which include sensory, motor and cognitive capabilities. Since this scale includes the subject's perception of their cognitive abilities, it is an important observation to report since the subjects not only did better on measures of everyday and working memory, they themselves felt like they struggled less than they had previously with their memory and problem solving.

The group analysis of the of the Adjustment subscale of the MPAI-4, which includes mood and interpersonal interactions demonstrated similar improvement (*P=.016*) following the aerobic exercise intervention. This finding is not unexpected since the Adjustment subscale includes many of the aspects of quality of life measurements. Very low quality of life has been commonly documented following TBI along with high rates of depression and anxiety.[99,100] And quality of life and mood has been shown to improve with the implementation of aerobic exercise in TBI subjects especially for the dosage of >90 minutes per week.[101]

The brief 8-item Participation Index serves as a useful measure of the final common aim—societal participation—of rehabilitation or other intervention efforts. Unfortunately, in the group analysis changes in the Participation subscale were not significant following the exercise intervention (*P=.13)*. This finding is not surprising

since the TBI subjects in this cohort were chronic in nature and their living and work situations were relatively fixed. Still, with the exception of Subject 5, all subjects did demonstrate improvement in this category. It is important to note that Subject 5 is the furthest in time (30 years) from the event of their original injury and that their community and social situation is relatively stable and intact.

3.4.6 Possible Mechanisms and Future Directions

This preliminary clinical study is the first to demonstrate the potential for use of aerobic exercise as an intervention to enhance cognition following TBI. It is also the first to link a human TBI population with the literature showing the positive effects of aerobic exercise on cognition. The findings of this study are supported by the physiological evidence that cortical changes have been found to occur following exercise. For example, regular physical exercise has been shown to stimulate brain vascularization through increase of blood flow and actual growth of new blood vessels (angiogenesis) especially in areas related to cognition such as the prefrontal cortex and hippocampus.[24-28]

Increases in brain catecholamines, particularly dopamine and noradrenalin have also been established following exercise and have been found to increase dramatically immediately post exercise.[102] Studies show that chronic wheel running in animals increases in noradrenalin and dopamine occur in several brain regions related to cognition as well as regulating synaptic plasticity and enhancing neuronal survival and promoting neural repair. They have also been implicated in the upregulation of BDNF.[89,103]

But even more conclusively, there is a distinct increase in brain derived neurotrophic factor (BDNF), which has been shown to improve neuronal survival and drive both neuro and synaptogenesis, especially in areas related to memory, like the hippocampus.[32,33,36,40] These changes in neuro and synaptogenesis have both been linked to specific areas related to cognition within the brain and also have been found to correlate with behavioral improvement in memory in animal populations.[32, 33, 36, 40] In animals, these physiologic changes have been shown to create a foundation for better memory, learning and overall cognitive performance.

The increase in some of the cognitive measures in this preliminary clinical study with TBI subjects are also consistent with findings demonstrated in rodents who have sustained TBI. A study by Griesbach et al. (2004) found exercise increased animal memory on the Morris Water Maze, as well as upregulating BDNF compared to sedentary animals.[24] In a more recent study by Griesbach, results determined that BDNF counteracted the cognitive deficits associated with the injury and provided evidence that BDNF indeed has a major role in exercise's cognitive effects in the traumatically injured brain.[45]

Why then might some TBI human subjects demonstrate improvement in their cognition following exercise while others do not? Even in neurologically intact populations, there is significant variability to the extent that cognitive performance improves following participation in exercise. This question is complicated and has yet to be studied extensively. Based on evidence, BDNF, dopamine and epinephrine appear to be the

mediators by which exercise may improve learning.

Recent literature has shown that there may also be a genetic link to whether the hoped for improvements occur and is currently centering around polymorphisms which can affect the catacholemines or BDNF.[104-107] These polymorphisms are of particular interest in the TBI population where it appears they may mediate the return of cognitive function.[106] Catechol-O-methyltransferase (COMT) is an enzyme that plays a crucial role in the metabolism of dopamine by deactivating it. The COMT gene contains a functional polymorphism called Val158Met. The Met allele is associated with a 3-4-fold reduction in the activity of the COMT enzyme, consequently increasing dopamine levels. In a study by Stroth et al., (2010) it was found that the Met-carriers outperformed their counterparts on tasks of inhibitory control and working memory compared to their Val-carrier counterparts.[104]

The Val66Met is the other polymorphism which may influence the effectiveness of exercise on cognition. Val66Met polymorphism of the BDNF gene interferes with intracellular trafficking, packaging and regulated secretion of the neurotrophin. The human prefrontal cortex shows lifelong neuroplastic adaptation implicating Val66Met BDNF polymorphism in the recovery of cognition following TBI. In a study by Erickson (2013), results revealed that the BDNF gene negatively impacted the effect of physical activity on cognitive performance, specifically, working memory.[107]

Therefore, more work needs to be done in a true randomized control trial to determine conclusively whether the limited effects in response to exercise found in this study can be

generalized to the greater TBI population as a possible intervention. In the next study, we will address what areas of the brain may be affected by the exercise intervention. In the future, however, it will also be important to tease out and determine what the underlying vascular, chemical and genetic physiological mechanisms truly are as well as whom the effects will benefit the most

3.4.6 Limitations of the Study

One primary limitation of this exploratory clinical study was the challenge of recruiting subjects. The unpredictability of the TBI population, intensity of the program (3 times each week for 12-weeks) and the requirement that subjects come to an urban medical center for the intervention may have contributed to recruitment difficulties. The original study power analysis recommended 32 subjects with randomization to experimental, sham, and control groups to determine an effect. The limited number of recruited subjects led to a re-design of the study which originally included a control group and sham condition into a single-group, pretest – posttest design. Internal validity for the new design may possibly have been impacted by the absence of a blinded, randomly selected control condition, the lack of multiple baseline cognitive testing, and not including a follow-up re-evaluation. Since all the subjects knew they were being studied and received the same exercise intervention with no repeated baseline testing, results may have been also influenced by a Hawthorne effect which is the tendency for subjects to perform better when they know they are expected to do so.

Another challenge to internal validity is also the potential for testing and learning effects

in regards to the outcome measures. This particular threat was attempted to be controlled by the use of cognitive measures with good test-retest reliability and little evidence of a learning effect in their validation literature. However, results of the PASAT should be considered cautiously due to the potential for a practice effect. Maturation or the general passing of time was also a potential danger to internal validity of this study. This problem could have been solved with multiple baseline testing to assure the stability of the cognitive status of each subject. Research has shown that most of the cognitive changes occur following TBI occur in the first year. To compensate for this threat the inclusion criteria required subjects to be at least one year post injury. Also it is important to note that the mean time since the subjects' injury was11.29 years thereby limiting the potential for spontaneous cognitive recovery. Threats to external validity and a challenge to the generalizability of all clinical studies of TBI include the inherent diversity in the subjects' history, mechanism of the subjects' injuries and variability in the cortical locations of their injuries. The possibility of observation bias is also a concern for this study since the investigator was not blinded. It is for the above reasons that the positive results found with this preliminary clinical study should be weighed carefully due to the limitations in the study design. The results demonstrating improvement in memory following aerobic exercise found within this preliminary clinical study are consistent with the findings of other studies in older adult and neurologically intact populations.

3.5. Summary

In summary, the findings from this exploratory study indicate that participation in a 12-

week aerobic exercise intervention did significantly improve selected measures of everyday memory, working memory and perceived disability in this small cohort of subjects with moderate-to-severe TBI. The demonstrated feasibility of a 12-week intervention in people with TBI, the observed safety of the treatment and testing procedures, and the improvements found in cognition in this pilot study all invite a larger randomized control trial in the TBI population to further explore these initial findings to determine whether aerobic exercise should be used as an adjunct intervention to improve not only cardiovascular fitness but cognition and functional outcome. This study also opens the door to investigate the potential changes in specified areas of the brain response to this intervention and whether injury to certain brain regions hinders treatment effects.

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CHAPTER IV

EFFECT OF AEROBIC EXERCISE ON BRAIN ACTIVITY FOLLOWING TRAUMATIC BRAIN INJURY

Summary

In Chapter II and Chapter III, the effects of aerobic exercise on every day, working memory, executive function and disability were explored. The purpose of this subsequent preliminary study was to describe a possible mechanism for the observed effects by exploring the changes in cortical activity through functional magnetic resonance imaging (fMRI) in individuals with chronic moderate-to-severe traumatic brain injury (TBI) following participation in a 12-week aerobic exercise intervention. **Methods:** A single-subject study design was implemented for this study. Seven males with moderate-to-severe TBI (mean age = 44.43 years, SD ±13.0), mean time since TBI (11.29 years, SD ± 11.12) completed a 12-week aerobic exercise intervention 3 days per week. A two standard deviation bandwidth method was used to analyze the dependent fMRI variables of voxel count, intensity and laterality index for individual subjects during the 0 back and 2 back working memory tasks. Regions of interest within the brain included the dorsolateral prefrontal cortex (DLPFC), precuneus, anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC). Secondary measures examined changes in aerobic capacity (VO_2 max) and accuracy and reaction time on the working memory tasks. A nonparametric Wilcoxon Signed-Ranks test was utilized to assess the differences between the subjects' aerobic capacity prior to and following the exercise intervention. The relationship between reaction time, aerobic intervention, and the accuracy and reaction time during the N-back tasks were evaluated with a mixed model with both fixed and random effects. **Results:** Aerobic capacity (VO_2 max) significantly improved over the 12-weeks (P = .016). Accuracy (P<.001) and reaction time (P=.009) also significantly improved on the N-back task of working memory following the aerobic

exercise intervention. fMRI intensity and voxel count findings were mixed. Subjects did demonstrate a trend toward left side activation of the DLPFC following exercise. Six subjects also demonstrated either significant or a trend toward increased precuneus intensity with a decrease in the number of activated voxels in the 2 back task compared with the 0 back task and an overall trend toward increased PCC activation and voxel count for both the 0 and 2 back tasks. **Discussion:** This study is the first to examine the effects of exercise as an intervention to promote plasticity following TBI. The results of this study indicate that a 12-week aerobic exercise intervention is associated with significant improvements in measures of aerobic capacity and working memory in subjects with moderate-to-severe chronic TBI. Data also suggests differences in brain activation following a 12-week aerobic exercise intervention in subjects with chronic TBI. Limitations of this study include a small sample size and lack of a control condition. **Conclusion:** These results indicate the need for future study in the TBI population with a randomized control trial to further explore the benefits of aerobic exercise as an adjunct intervention to improve not only cardiovascular fitness but cognition and brain activity. **Key Words:** Working memory, Exercise, Brain Injury, fMRI.

4.1. Introduction

Traumatic Brain Injury (TBI) often causes long-lasting issues with working memory and executive function that have been shown to limit the return to everyday normal functioning. These enduring cognitive impairments not only impact the lives of TBI

survivors, but also the lives of significant, the community and health care system.[1] It has been determined that cognitive function depends on an integrated, distributed network of brain connectivity.[2-6] The individual activity and interaction of the specific brain regions within each network and the relationships between the networks themselves are important underlying components of efficient cognitive function.[4-7] These critical networks include areas activated by tasks requiring attention and working memory (task-positive networks), as well as a set of brain regions that show highly correlated activity during "rest" and a reduced level of activation during the most attentionally demanding tasks.[3,4,8,9] Over time, it is becoming apparent that a detailed understanding of the effects of injury on these networks may be an important piece of the puzzle in the development of rehabilitation strategies.

4.1.1. fMRI Activation and Deactivation

fMRI measure is an indirect measure of brain activity. A static magnetic field is created by the MRI scanner. This scanner uses a series of changing magnetic fields and oscillating electromagnetic fields, known as the pulse sequence. The pulse sequence is adjusted for properties of hydrogen nuclei. The hydrogen nuclei in water that composes a large component of most living systems also has magnetic properties or a magnetic moment due to the "spin" of the protons.[10] The magnetic field within the MRI magnet results in some of the protons aligning with the magnetic field causing the aligned spins to "precess" or circularly spin as a group, like a top. By applying a pulse with the same frequency as the precession, the spins are changed until they are perpendicular to the

main magnetic field causing a voltage change. After the completion of the pulse, the spins return to their original orientation, referred to as 'relaxation times'. The relaxation times release energy or voltage that is detected through a coil around the imaged subject.[11]

The most common type of fMRI signal is based on the blood oxygenation level dependent (BOLD) contrast. Energy cost for neuronal activity results in increased local blood flow as a direct consequence of neurotransmitter action.[12] The assumption in BOLD fMRI is that increases in local blood flow leads to an increased ratio of oxyhemoglobin to deoxyhemoglobin in the region of neuronal activation. The majority of brain tissue receives more oxygen than is metabolically necessary, resulting in an oversupply of oxygen especially in the region of greater synaptic activity.[13] Because oxygenated hemoglobin has no unpaired electrons, it is diamagnetic and has no magnetic moment. Alternatively, deoxygenated hemoglobin has unpaired electrons and therefore has the property of being attracted to a magnetic field.[12] The contrast in MRI is based on the 'relaxation times' (T) of the spinning protons. T1 is dependent upon the return of longitudinal magnetization and T_2 and T_2^* are the time constants in transverse magnetization.[12] BOLD fMRI primarily depends on the T_2^* effects. Therefore, in the area of tissue that has an increase in oxygenated hemoglobin, T_2^* will be longer, resulting in a signal increase with respect to the baseline.[12] As explained above, fMRI is an indirect measure of neural activity, but significant correlations between the BOLD contrast and neural activity were found in both the local field potential and the neuronal firing rate, thereby confirming that the BOLD signal reflects neural activity.[14,15]

Functional connectivity can be studied either during the performance of a task, or in the absence of an externally imposed task ('resting state' fMRI). The BOLD response is not always positively correlated to the stimulus time-course the way it has been described so far. Negative signals (anti-correlations) have also been observed and reported (Figure 1).[9,14] fMRI studies have shown that certain brain regions consistently show greater activity during rest than during a cognitive task and are in fact anti-correlated (4.2. A and B). This finding has led to the hypothesis indicating the existence of a network of activated (task positive) regions and deactivated (default mode) regions that are integral tocognition.[9]

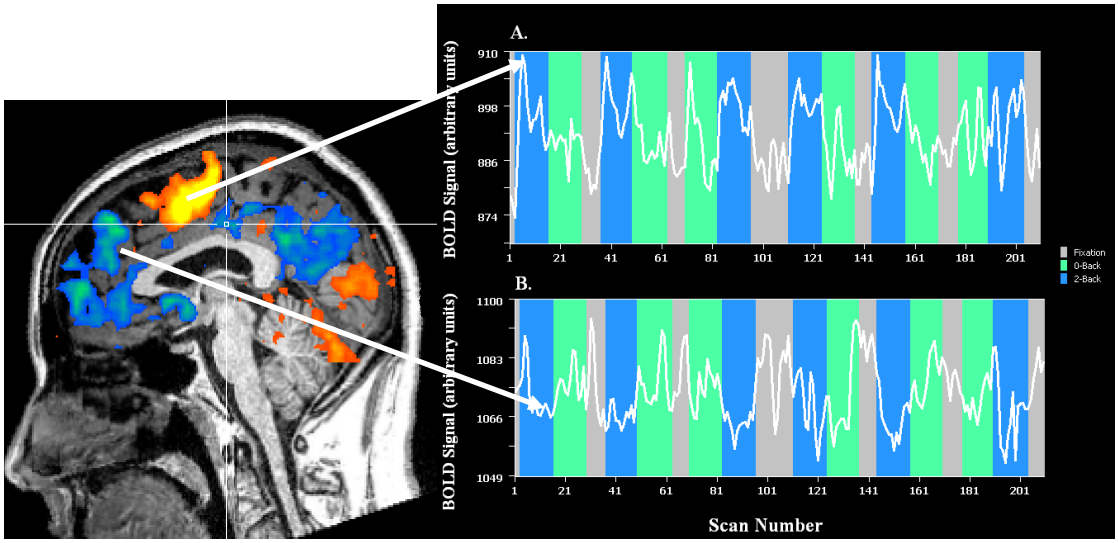

Figure 4.1 Example of activation and deactivation and (B) during the 2 back task. Red/yellow indicates activation. Blue/green indicate deactivation.

Figure 4.2. Example of BOLD signal (A) activation deactivation during the same task 2 back task.

4.1.2. Task Positive Network for Working Memory

Current theories propose that the prefrontal cortex provides top down signals that modulate incoming sensory information during working memory tasks. As the

processing becomes more complex, it becomes necessary for the posterior parietal cortex to become activated as well. [3,16-18] The region of the prefrontal cortex that has been highly correlated with working memory tasks is the dorsolateral prefrontal cortex (DLPFC). Participation of the DLPFC in working memory has long been established in primates using single-unit recordings, and in normal human adults using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).[19-23] During fMRI, DLPFC activation at or near Brodman's Areas (BA) 9 and 46, has been found to occur during tasks that require organization of items that are active in working memory.[23-25] DLPFC activation has been found to directly support subsequent long-term memory formation and learning.[23]

The posterior parietal area linked with the DLPFC during cognitive and specifically working memory tasks is the precuneus (BA 7). Until recently, the precuneus has received little attention. In the diffuse tensor imaging (DTI) studies, it has been found that the BA 7 has extensive links with the prefrontal lobes and especially with BA 9 and 46 (DLPFC).[26-29] Surprisingly, these studies demonstrate no direct connections of the precuneus with the primary sensory regions. Because of this, it is reasonable to assume that precuneus activity is involved in clarifying associative information rather than processing external sensory stimuli.[30]

The role of the precuneus in higher level cognitive function and particularly memory retrieval has also been established in positron emission tomography (PET) and fMRI. [31-35]

In 2008, Srimal and Curtis further elaborated the role and connectivity of the precuneus during a memory guided saccade (MGS) task.[36] Using fMRI, researchers were able to measure persistent neuronal activity in the DLPFC and precuneus during a delay in the task. This finding serves as compelling evidence that this activity may reflect a form of memory representation.[36] This finding was again reproduced in fMRI studies where it was also discovered that the magnitude of the blood-oxygen-level-dependent (BOLD) activity in the DLPFC and precuneus predicted accuracy in the memory task.[37] Finally, coupling and functional connectivity of the DLPFC and precuneus was demonstrated during the N-back working memory task using regional cerebral blood flow techniques (rCBF).[6] Together, these results strongly indicate that the persistent activity between the DLPFC and precuneus form a bridge linking the prior stimulus with the contingent response. The precuneus has demonstrated strong network connections with the DLPFC.[34] In a study by Bledowski et al., (2009), it was determined that both the DLPFC and precuneus increase in activation with greater task difficulty. In a later study, by Hillary et al., (2011), it was found that the connectivity between the DLPFC was further elucidated by the finding that healthy subjects exhibited an anterior (DLPFC) to posterior (precuneus) shift with greater task practice.[38]

The cingulate cortex has also been highly implicated in higher level cognition. The anterior cingulate (ACC) has been suggested as a monitoring center that is responsible for online detection of response conflicts. Stimulus-Response (S-R) compatibility is the naturalness of the connection between the stimulus and the associated response. Reaction time for skill performance is faster the more compatible the S-R pairs. For

example, the S-R compatibility for turning a car steering wheel to the left in response to an upcoming left turn stimulus is very close. However for a sailing boat the response would be the opposite, or an incompatible response thereby creating a conflict. Based on this theory, ACC activation should be greater following incompatible trials than following compatible ones. This prediction was confirmed in an fMRI study of the flanker task, the results of which have recently been replicated and extended. [39,40] It has also been suggested that the ACC and DLPFC are responsible for both anticipatory preparation and online adjustment in response to conflicts between incompatible stimuli.[41] The posterior cingulate cortex (PCC) has also been shown to be a contributing region in the network related to attention and working memory and a relatively new area of interest. Interestingly, the PCC often shows consistent deactivation when attention is focused on external events and greater activation at rest.[7] fMRI studies of attentionally demanding tasks also show a relative deactivation as task difficulty increases.[3] In contrast, functional connectivity analyses reveal a clear dissociation between the caudal ACC and the PCC. As task difficulty increases, the caudal ACC shows increasing activation (potentially due to greater conflict) and the PCC shows the opposite pattern. The literature results provide evidence that the PCC may be involved in internally directed thoughts.[7]

4.1.3. DMN for Working Memory and Executive Function

As previously mentioned, fMRI studies have shown that certain brain regions consistently show greater neural activity during rest and then show a relative *deactivation*

during a task. Functional connectivity can be studied either during the performance of a task and during the absence of an externally imposed task (resting state). During these studies, high level, task specific networks have been identified. These networks include brain regions activated by tasks (task positive networks) as well as brain regions that show reduced levels of activation during the most attentionally demanding tasks.[8,9]

The normally deactivated cortical regions for cognitive tasks are commonly referred to as the Default Mode Network (DMN).[8] In health controls, the DMN will be disengaged during the periods of externally focused attention (during the task). This deactivation of the DMN has also been found to be anti-correlated with the predominantly right-lateralized, task-positive, fronto-parietal network during attentionally demanding tasks.[7,9] As an example, when the brain is supposedly at "rest" it is really not resting, but thinking of a multitude of internally driven thoughts or "daydreaming". When we are asked to concentrate on a difficult task, the DMN demonstrates a subsequent decrease in activation while the task-positive network shows a correlated increase.

The task positive network includes the cortical areas of the DLPFC, precuneus and the ACC. The correspondingly deactivated DMN includes the medial prefrontal cortex and the posterior cingulate cortex (PCC). For example, the PCC shows an inverse relationship in activity to the DLPFC during a working memory task.[9] Overall, it appears the tenuous relationship between the deactivation/DMN and the task

positive/fronto-parietal networks are important to consider when studying working memory efficiency.

4.1.4. Differences in TBI Brain Activation

It is well known neuroimaging studies following TBI consistently support the idea of prefrontal cortical dysfunction even without evidence of structural brain lesions in the region.[42-44] Following moderate-to-severe TBI, attention and working memory impairments are nearly universal resulting in a failure to maintain consistent goal-directed behavior. Current literature indicates that subjects with moderate-to-severe TBI also show differing patterns of brain activations in the task-positive network and the DMN than healthy subjects during the same tasks. In a study of subjects with mild TBI and no evidence of lesion through neuroimaging, subjects showed a more diffuse pattern of activation and load related differences in areas related to task-positive activation during an auditory N-back task of working memory compared to uninjured controls.[45] As processing load increased, TBI subjects showed a disproportionately large increase in activation of the task-positive network compared to controls especially in the right dorsolateral prefrontal and parietal cortices.[46] Furthermore, the functional connectivity of the precuneus was found to predict which subjects go on to have persistent cognitive impairments.[47]

Studies have also found the DMN to be abnormally active and the balance between the DMN and the fronto-parietal network disrupted following TBI.[45,48-53] These studies have

also shown that the abnormal increase of activity within the DMN was correlated to decrements in performance during attentionally demanding tasks and has been linked to "mind wandering," distractibility and mental fatigue.[7,47,52,54] TBI often results in diffuse axonal injury, which produces cognitive impairment by disconnecting nodes in distributed brain networks. These results show that abnormalities in the fronto-parietal and DMN networks are sensitive markers of cognitive impairments following TBI.

Overall, the number of studies and the underlying functional correlates regarding differing patterns of DLPFC, precuneus, and PCC activity in TBI subjects compared to uninjured controls is limited. This limitation, along with the inherent heterogeneity of TBI itself, makes definitive conclusions difficult. Although recent findings are encouraging, there continues to be a paucity of literature regarding brain function following TBI. It therefore becomes essential to address this gap by both improving the understanding of brain functions following TBI and exploring interventions that may physiologically enhance brain function and cognition.

The purpose of this study was to evaluate effects of a 12-week aerobic exercise intervention on the brain activity involved in a working memory task in moderate-to-severe TBI subjects. There is both theoretical and practical significance for conducting this study. On a theoretical level, this study will integrate many areas of science including exercise physiology and neuroscience to enhance the understanding of the distant effects of aerobic exercise beyond the commonly acknowledged physiological effects. To my knowledge, there have been no studies of the effect of brain activity

during a working memory task following participation in an aerobic exercise intervention in persons with TBI. Thus, the primary purpose of this preliminary clinical study was to describe changes in cortical activity of the DLPFC, precuneus, ACC and PCC in individual subjects with chronic moderate-to-severe TBI following participation in a 12-week aerobic exercise intervention. Based on previous literature, directional changes were determined for each of the hypotheses. We also assessed the influence of exercise on the secondary measures of the accuracy and reaction time of the working memory task. The aims and hypotheses for this study include the following;

Aim 1 $_{B.1)}$ To ascertain the type of changes that occur in the cortical activity of moderate-to-severely injured TBI subjects following participation in a 12-week aerobic exercise intervention. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1. $_{B.1)}$ An decrease in the fMRI voxel count indices and signal intensity within the dorsolateral prefrontal cortex (DLPFC) and precuneus to occur during the 2-back task.

H.2. $_{B.1)}$ A decrease in the fMRI voxel count index and intensity of the ACC and PCC to occur during all N-back tasks.

H.3. $_{B.1)}$ A more positive laterality index indicating greater left hemispheric involvement during all N-back tasks.

Aim 2. $_{B.2)}$ To determine the extent of improvement in cardiovascular capacity of moderate-to-severely injured TBI subjects following participation in a 12-

week aerobic exercise program. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.$_{B.2.)}$ A significantly greater maximal oxygen uptake to occur during a maximal graded treadmill test as measured by an increase in VO_2 max.

Aim 3. $_{B.3)}$ To determine the extent of working memory improvement in moderate-to-severely injured TBI subjects following participation in a 12-week aerobic exercise intervention. Following participation in a 12-week aerobic exercise intervention, I hypothesize:

H.1.$_{B3.)}$ A decrease in reaction time to occur during the N-back tasks.

H.2.$_{B3.)}$ An increase in accuracy to occur during the N-back tasks.

4.2. Methods

4.2.1. Study Design

A single-subject AAA-B-AAA (A= measurement, B=intervention) study design on multiple subjects was implemented for this study and was used to analyze the dependent fMRI variables of voxel count index, intensity and laterality index for each subject. A single-subject design with a systematic collection of repeated measurements represents an alternative to traditional group comparison statistics used for the evaluation of clinical interventions.[55] The demands of traditional experimental methods can become barriers to rehabilitation research especially in clinical populations, like TBI. The exploration of inter-subject and intra-subject variability and the allowance for real-time, continuous

monitoring of change are advantages of single-subject research designs which assist in making the findings more clinically relevant.[55-57] Most importantly for this study, a single subject approach assisted with overcoming difficulties inherent in recruiting large numbers of TBI subjects. The single-subject approach provides a means to compare the effect of an intervention in a small number of study participants and also allow a more in depth and individual analysis of the findings.[57] An additional benefit includes the design's insensitivity to weak treatment effects since it ensures that only large treatment effects with large significance will be reported.

IRB approval was obtained through The University of Minnesota, the Minneapolis Veteran's Administration Medical Center, and Healtheast Bethesda Hospital. A further assessment of the subject's decision-making capacity was determined through a Modified Dysken Screening Tool. The assessment tested whether the subjects could both understand and provide informed consent. Per IRB recommendation, potential research subjects were required to answer at least 70% of questions correctly in order to have sufficient understanding of the study to provide informed consent. All seven subjects were legally competent and were able to understand the consent form as determined by the screening tool.

4.2.2. Subjects

A convenience sample of seven TBI adult males (mean age 44.4 years, SD ±13.0, range 28-60 years, mean total years of education 13.57 ±1.4, range 12-16 years) were recruited from the Minneapolis Veteran's Administration Medical Center in Minneapolis, MN, and

Healtheast Bethesda Hospital in St. Paul, MN. Subjects were recruited through posted flyers and brochures, therapist recommendation, and via a letter sent to Minneapolis VA TBI outpatient clinic participants. A CONSORT flow table (Table 4.3) describes the history of subject recruitment and participation.

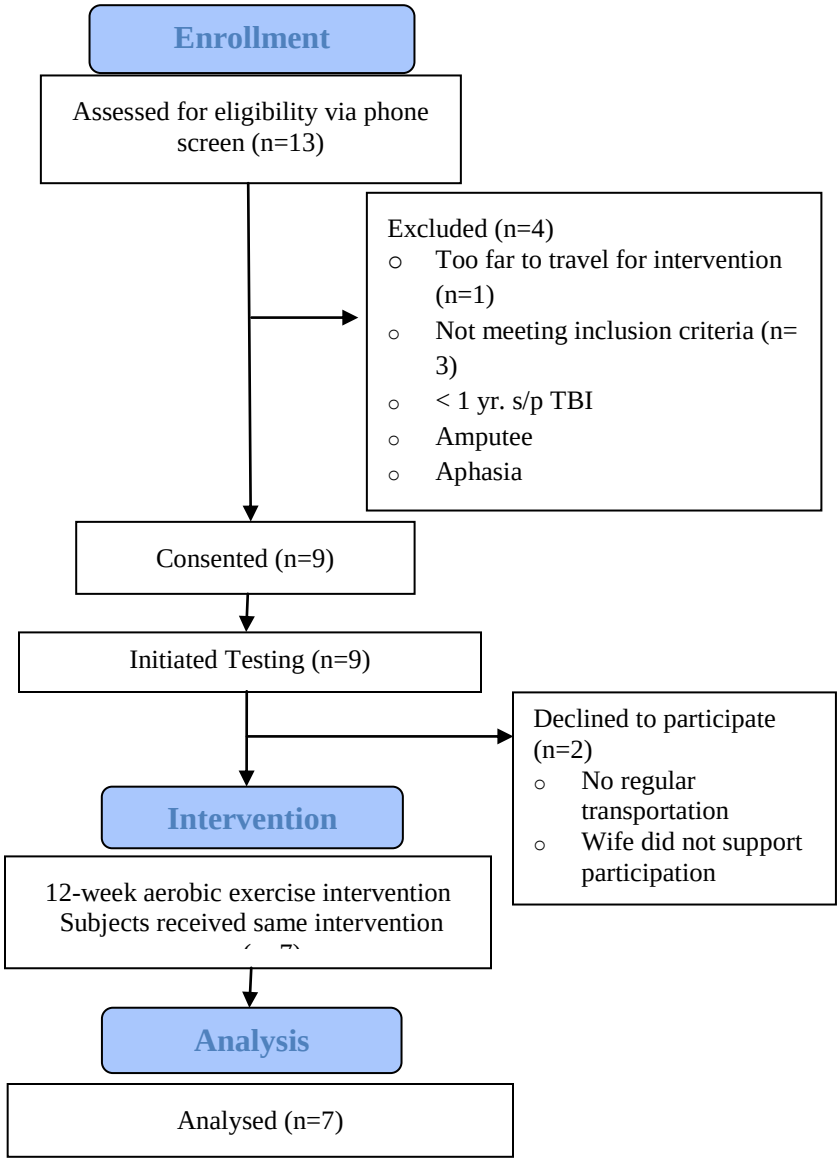

Figure 4.3. CONSORT Flow Diagram.

Subjects were community dwelling outpatients who presented sub-acute, moderate-to-severe, non-penetrating TBI and were at least one year post-injury. Injury severity was determined based on available data as follows: "moderate" if the patient had a Glasgow Coma Scale (GCS) score between 9 and 12 and loss of consciousness (LOC) between 30 minutes to 24 hours. "Severe" if the LOC was for > 24 hours and they had a Glasgow Coma Scale (GCS ≤ 8). Post-traumatic amnesia time was required to be > 1 hour. The time since injury was a mean of 11.29 years (SD ± 11.12 years, range 1-30 years). Chart reviews were completed on each subject to determine the location and etiology of their injuries as well as their LOC length. (Table 4.1 includes the demographic data for each subject).

Inclusion criteria included:

- Non-penetrating traumatic brain injury > than 1 year post injury.
- Between ages 18 and 60 years of age.
- Moderate-to-severe traumatic brain injury (TBI) evidenced by a Glasgow Coma Score of 3-12, within 72 hours of injury.[58]
- Legal competence
- Post-traumatic amnesia time of > 1 hour
- Current a Rancho Los Amigos Cognitive Scale score ≥ VII to allow for adequate participation in the cognitive testing.
- Mini Mental Status Examination score > 22. Vision correctable to 20/40.
- Ability to ambulate >150' with or without an assistive device.

- Berg Balance Score ≥ 45 to minimize fall risk
- >45° index finger flexion and extension to allow pushing a button
- Subjects or caregivers report of difficulties in executive functioning or memory.
- MD consent

Exclusion criteria included:

- Penetrating brain injuries
- Currently participating in a regular exercise program within the last 3 months or currently enrolled in rehabilitation.
- Visual field disturbances.
- Previously diagnosed psychiatric illness as defined by DSM: Axis I Clinical Syndromes.
- Agitation
- Previously diagnosed developmental disability
- Previous myocardial infarction, cardiac pacemaker, angina, cardiac arrhythmias, aortic stenosis, pulmonary embolus, uncontrolled hypertension, acute or chronic infectious disease or uncontrolled metabolic disease.
- Depression determined by a Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15. [59]
- Subjects could not have current substance abuse issues as determined by the CAGE Questionnaire for Alcohol Screening and MPAI pre-existing conditions questions. [60,61]
- Abnormal graded treadmill exercise test.

Exclusion criteria for fMRI included:

- Cardiac pacemaker
- Aneurysm clip
- Implanted cardiac defibrillator, any type of biostimulator or any type of implanted electrodes
- Cochlear implant.
- Implanted insulin pump or implanted drug infusion device.
- Catheter.
- Halo vest or cervical fixation device.
- Hearing aid.
- Any foreign body (i.e.; shrapnel, bullet, heart valve prosthesis, any type of ear implant, eye prosthesis, any surgical clips or staples, vascular access port, intraventricular shunt, artificial limb or joint, dental hardware i.e.; braces, retainer, IUD, wire mesh, any orthopedic implants: pins, rods, screws, nails, etc., or non-removable body piercing).

Table 4.1. Subject demographics.

Subject	Age	Yrs. since injury	Yrs. of educ.	Type/location of TBI	GCS	Injury Severity	Etiology	RLA Score	MMSE	Berg Balance Score	PHQ-9
1	28	5.75	12	Bilateral cerebral contusions, Diffuse axonal injury	3	Severe	Motor Vehicle Accident	7	24	50	2
2	60	7	14	Left frontal subarachnoid hemorrhage	9	Moderate	Motor Vehicle Accident	9	28	52	7
3	35	1.3	12	Right frontal subdural hematoma, Diffuse axonal injury	3	Severe	Motor Vehicle Accident	7	23	48	5
4	32	11	14	Right frontal subdural hematoma	3	Severe	6 ft. fall	9	30	56	2
5	51	30	13	Bilateral cerebral contusions, Diffuse axonal injury	10	Moderate	Motor Vehicle Accident	10	30	56	0
6	59	1	14	Right frontal & parietal subarachnoid hemorrhage	3	Severe	Assault	9	27	52	5
7	46	23	16	Left temporal subdural hematoma	3	Severe	Softball to head	7	29	46	7

GCS = Glasgow Coma Scale score < 72 hours post injury(max 15), RLA = Rancho Los Amigo Scale of Cognitive Functioning level (max 10), MMSE = Mini Mental Status Exam score (max 30), Berg Balance Score (max 56, PHQ-9 = Patient Health Questionnaire-9 (max 27, > 15 indicates depression).

Table 4.2. Subject, substance use, living and work situations.

Subject	Substance Use as determined by CAGE Questionnaire and MPAI pre-existing conditions	Living Situation	Work
1	Previous ETOH abuse. Has not used since injury.	Lives with parent	Sheltered workshop
2	Previous ETOH dependence. Has not used ETOH in 34 yrs.	Lives independently	Retired
3	Previous ETOH abuse. Has not used since injury	Assisted living	Not employed
4	Previous drug/ETOH abuse. Has not used since injury	Lives independently	Paid employment
5	Previous cannabis/ETOH abuse. Has not used ETOH since 1990. Currently not using cannabis	Lives independently	Paid employment
6	Previous drug/ETOH abuse, has not used since injury	Lives with significant other	VA work program
7	Never used drugs or ETOH.	Home health assistance	Volunteer work

ETOH = alcohol. MPAI = Mayo Portland Adaptability Inventory.

4.2.3. Outcome Measures

Measures were assessed at baseline and after 12-weeks of participation in the aerobic exercise intervention. fMRI testing took place at the University of Minnesota Center for Magnetic Resonance Imaging (CMRR). Subjects were tested in the fMRI on three separate occasions both prior to and three times following the completion of the exercise intervention. Each of the three trials took place during the same week and approximately at the same time of day (Table 4.3).

Table 4.3. Schedule of subject testing.

	Day 2	Day 3	Day 4	12-weeks	Day 1	Day 2	Day 3	Day 4
Treadmill Test	Pretest fMRI 1	Pretest fMRI 2	Pretest fMRI 3	Exercise Intervention	Posttest fMRI 1	Posttest fMRI 2	Posttest fMRI 3	Treadmill Test

fMRI = Functional Magnetic Resonance Imaging.

Cardiopulmonary maximal treadmill testing was once at pretest and once at posttest. The treadmill testing was performed by a trained technician at the University of Minnesota Clinical and Translational Science Institute or the Veteran's Administration Medical Center cardiac lab in Minneapolis.

Assessment of Aerobic Capacity

To assure that subjects improved their aerobic capacity a maximal treadmill test using a modified Balke-Ware treadmill protocol was performed by a trained technician at the University of Minnesota Clinical and Translational Science Institute or the Veteran's

Administration Medical Center cardiac lab in Minneapolis both prior to and following the 12-week exercise intervention. During the test, subjects wore a non-rebreathing mask and nose plugs while a metabolic cart was used to collect expired gases. Subjects also wore a blood pressure cuff and a 12-lead electrocardiogram (ECG) to monitor blood pressure, heart rate, and rhythm. After becoming familiarized with the treadmill, subjects walked at 3.3 mph at 0% grade for three minutes with the grade then increasing by 2.5% every two minutes. Subjects were closely guarded and allowed to use the handrail to minimize risk of falling. Maximal effort was identified by the following criteria: a respiratory exchange ratio (RER) of 1.15 or more, a failure to increase heart rate with increases in exercise intensity, a plateau in VO_2, +/- 10 beats/minute (bpm) above age predicted maximum heart rate, or subject fatigue.[63] This modification of the original Balke-Ware protocol has been previously used in persons with TBI.[62] Cardiovascular stability was measured continuously through changes in heart rate and rhythm via a 12-lead ECG. Participants were also monitored every minute with Borg's Rating of Perceived Exertion Scale to assess perceived effort.[64-67] VO_2 (oxygen consumption) was measured every 15 seconds via a non-rebreathing mask. Gas and treadmill calibrations were performed on the equipment prior to each test. American College of Sports Medicine guidelines were used to determine whether the testing should terminate prior to completion of the test.[63] These criteria included ST depression more than 2 mm, increasing nervous system symptoms, sustained ventricular tachycardia, chest discomfort, and +/- 10 beats over age predicted maximal heart rate. The peak heart rate, exercise duration, peak aerobic capacity (VO_2 max) and RER were monitored and recorded during the exercise test. VO_2

max refers to the maximum amount of oxygen that an individual can utilize during intense or maximal exercise. It is measured as milliliters of oxygen used in one minute per kilogram of body weight.[63] VO_2 max has been shown to be the most accurate measurement of functional capacity and is an indicator of overall cardiopulmonary health.

fMRI Testing

In this study there were three common measures used for classification of task-related activity changes following fMRI analysis. The first was the change in the volume of activation, called the voxel count with a 'voxel' being defined as an individual, 3 x 3 x 3 mm cuboid element in the brain .[12] The second was the change in BOLD signal intensity during task performance vs. the baseline.[10,11] The third was the change in the laterality index (LI) based on significantly active voxel counts. LI describes both the hemispheric predominance (right, left, bilateral activation) and the degree of lateralization (how strongly left or right).[69-70]

Within the fMRI scanner, subjects were instructed in a working memory task (N-back task) and allowed to practice until 70% competency was achieved in the 0-back task outside of the fMRI scanner. All subjects were imaged on three different days during the same week both prior to and following completion of the aerobic exercise program. Images were taken using a 3-Tesla whole body magnetic resonance scanner (Magnetom Trio, Siemens, Munich, Germany) equipped with a standard twelve channel head coil to collect data. A localizer scan was administered first to select the volume of brain to be

studied. Next, a high-resolution ($1mm^3$), T1-weighted, three-dimensional (3D) anatomical image dataset (3D MP-RAGE, TE/TI/TR = 2.5/1000/2150 ms, FA = 8°, GRAPPA R=2, total acquisition time = 4:58) was obtained over the entire brain to identify appropriate regions of interest (ROIs). This image then served as a template for the functional images, which was overlaid during later analysis. $T2^*$-weighted fMRIs of the BOLD signal were taken in the transverse plane with a gradient echo-planar imaging sequence (echo time, 30ms; TR, 3000 ms; FA, 80°; field of view, 192 x 192 mm with a matrix size of 64 x 64). A total of 145 scans were taken of the selected brain volume, divided into 36 slices, with each slice 3 mm thick. The resultant voxel resolution was 3 * 3 * 3 mm. These images were taken while the subjects performed the N-back tasks as described in Fig. 4. And 4.7.[71] The total imaged volume extended from the superior pole of the cortex to a depth of 108 mm in 36 interleaved slices. During the experiment, a block fMRI design was used whereby 195 brain scans were acquired for a total scan time of 9 minutes and 45 seconds which covered the time for all the alternating fixation/0-back/2-back blocks.

Working Memory Task

Subjects were required to perform the N-back working memory task using E-Prime Version 1.1 visual presentation software while lying supine in the 3T scanner. During fMRI imaging, the instructions and N-Back task were projected from a computer onto a mirror outside the scanner to a screen which could be viewed by the subject through a rearview mirror mounted on the head coil (see Fig 4.4).

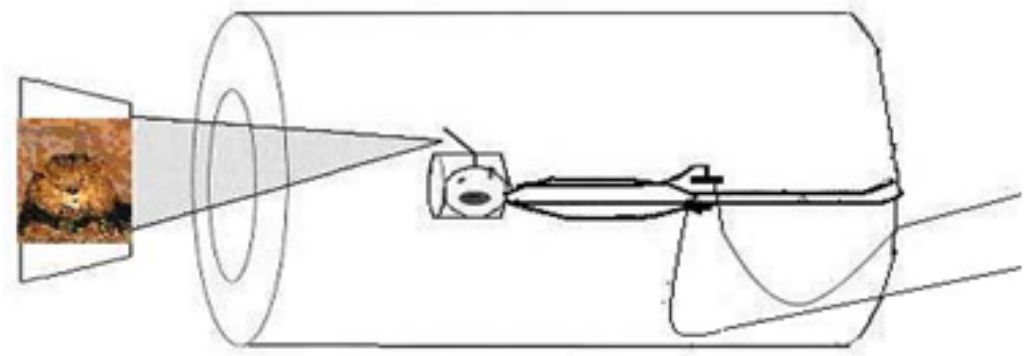

Figure. 4.4. Functional Magnetic Resonance Imaging (fMRI) set up for N-back task.

During the N-back task, subjects experienced three conditions: visual fixation, 0 back task, and 2 back task. There were 6 pseudo-randomized blocks of a 0 back and 2 back task combination. Each block included 15 response stimuli for each task. Each block was also preceded by and ended with a fixation condition for a total time of 9 minutes and 45 seconds (Fig. 4.5).

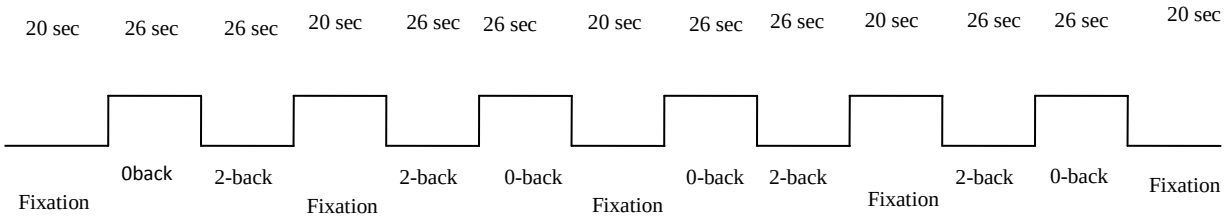

Figure. 4.5. Example of the timing and order of pseudo-randomized N-back block conditions.

For the fixation (control) condition subjects were asked to view a + on a screen for 20 seconds. No motor response was required. For the 0-back (Fig. 4.6) and 2-back (Fig. 4.7) working memory conditions, 15 pictures of animals were presented during each of

the 6 blocks. Each animal picture was shown for .5 seconds with an immediate response time lasting 2 seconds. For the 0-back condition, subjects were asked to press a blue response button located on a 2 X 3 inch box in their right hand if a lion was presented on the screen or to press a red response button located on a 2 X 3 inch box of their left hand if the picture on the screen was not a lion. For the 2-back condition subjects were asked to press the response button on the right if the animal presented on the screen matched the picture of an animal presented two animals back. Button boxes were attached by non-magnetic cords to a laptop computer in the fMRI control room where subject accuracy and reaction times were logged into E-Prime.

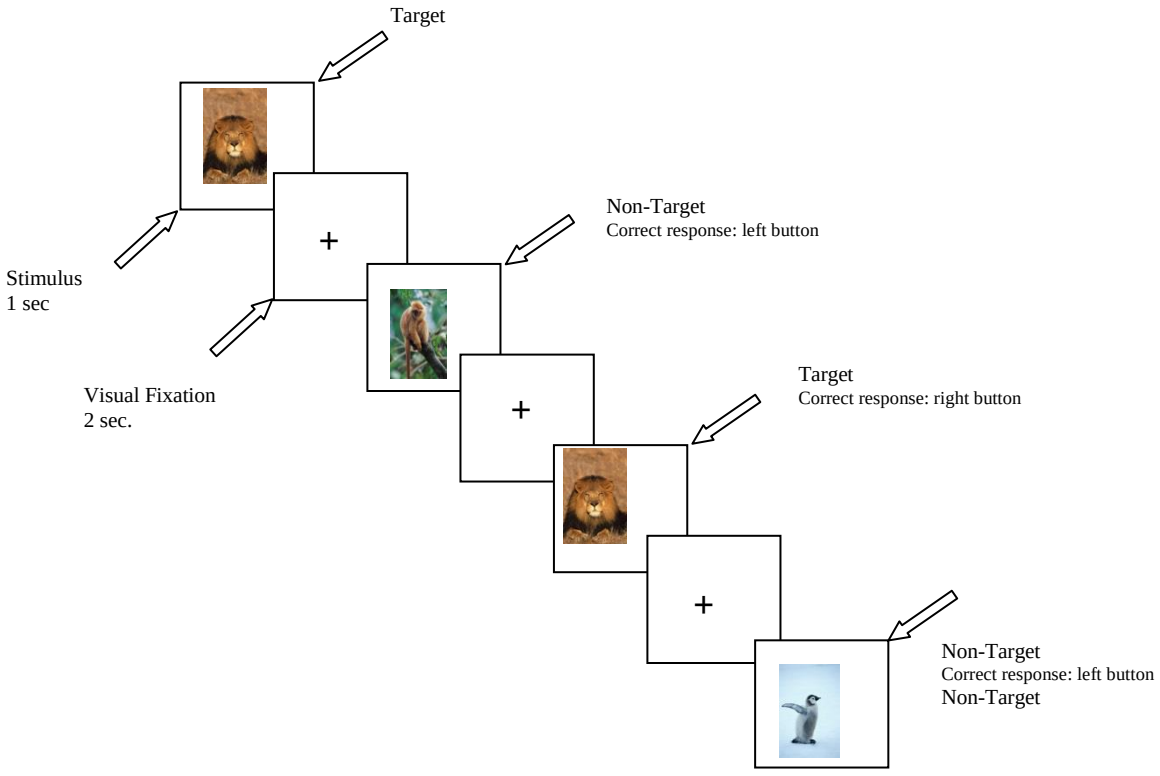

Figure. 4.6. Example of the N-back task stimuli for the 0- back condition. The subject is instructed to press the right button whenever the target picture (Lion) is presented and left button when it is not a lion This series only represents a fraction of the sequence comprising one block of the 0 back condition.

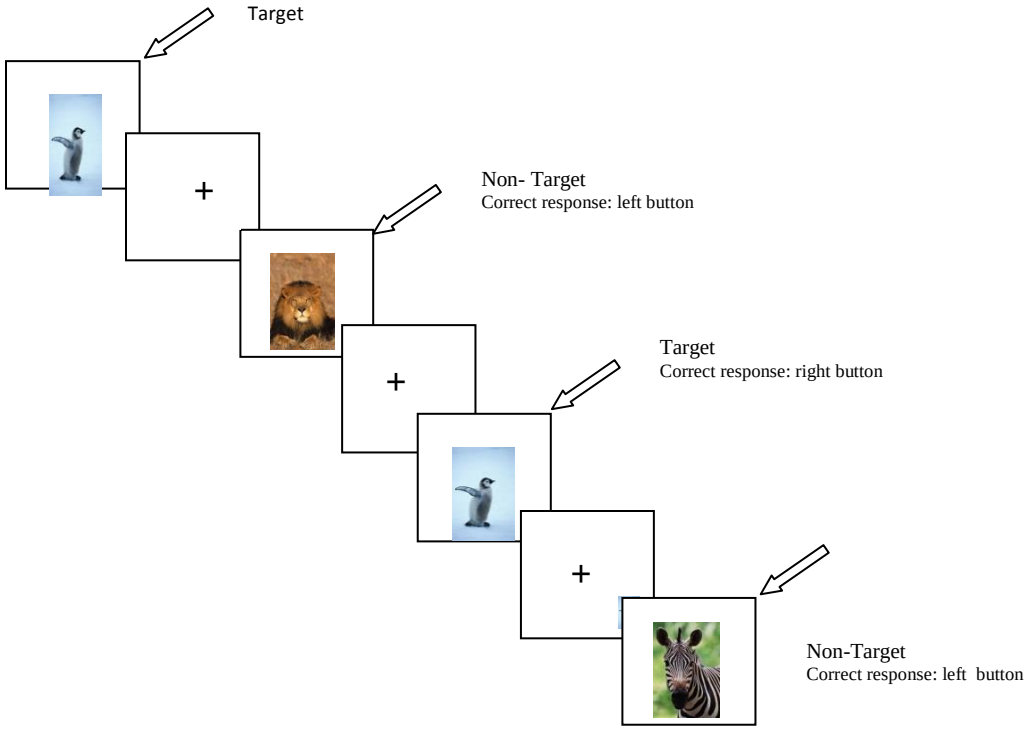

Figure. 4.7. Example of the N-back task stimuli for the 2 back condition. The subject is instructed to press the right button whenever the target picture is the same a two pictures back. Subject presses the left button when it is not the same animal presented as two pictures back. This series only represents a fraction of the sequence comprising one block of the 0 back condition.

4.2.4. Imaging Data Analysis

Brain Voyager QX (Brain Innovation BV, Maastricht, the Netherlands) software was used for fMRI data preprocessing and analysis. Images were pre-processed to correct for head motion artifacts, differences in slice scan time acquisition, and temporal linear trends. Anatomical images were co-registered with the functional images using anatomical landmarks. Anatomical and functional images were both were normalized to standard Talairach space. Boxcar waveforms were merged with the hemodynamic response function and synchronized with individual response times were used to model the control, 0 back and 2 back tasks. Differences in BOLD signal intensity for the three

tasks were analyzed for each subject using a general linear model (GLM) with 9 predictors. One predictor compared the 0 back task to the control condition, the next predictor compared the 2 back task to the control condition and then 2 back activity was compared to the 0 back. The last six predictors accounted for translational and rotation movement in all three planes and were entered as covariates to exclude the influence of movement artifact on the BOLD signal. The data collected from the GLM included the active voxel count (volume) and the average BOLD signal intensity, calculated as the average t statistic of the difference between the predictors for each participant and each ROI. These statistics were determined using a false discovery rate (FDR) of q(FDR) <.05 as a significance level.

Dependent fMRI Measures

Individual analyses were performed based on individual subject's anatomy because brain normalization after a head injury raises methodological problems due to alterations in brain structure. For each participant, individuals manually drew regions of interest (ROIs) on anatomical images in each hemisphere of the DLPFC, ACC, PCC, and the precuneus. ROI's were assessed for voxel count, signal intensity and laterality index. The voxel count signifies the volume of significantly activated or deactivated voxels within the defined ROI between each relevant predictor. The signal intensity is determined through the average t statistic reflecting the difference in intensity for a given significantly activated or deactivated voxel within a defined ROI between each relevant predictor across all measurement points for that voxel. The laterality index (LI) was

determined for volume only and was calculated for each ROI by the formula: [($Volume_{left}$ – $Volume_{right}$)/ ($Volume_{left}$ + $Volume_{right}$)]._ A value of +1.0 indicates complete left hemisphere activation, a value of 0 indicates equal activation between hemispheres, and a value of -1.0 indicates complete right hemisphere activation.[69-70] Completed drawings and entered data were reviewed by the primary investigator and one peer to ensure accuracy and consistency.

The DLPFC ROI's were drawn in the coronal plane in the format standardized by Sanches et al. (2009).[72] The anterior border was determined to be one slice posterior to the frontal pole. The medial border was located above the cingulate sulcus without including the cingulate gyrus. The posterior border was determined to be immediately anterior to the most rostral slice where the anterior commissure can be seen. The inferior border was determined to be the inferior frontal sulcus. (Fig. 4.8 and Fig. 4.9)

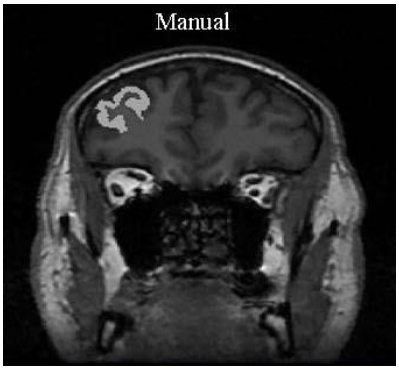

Figure. 4.8 Trace of DLPFC in the coronal view.[58]

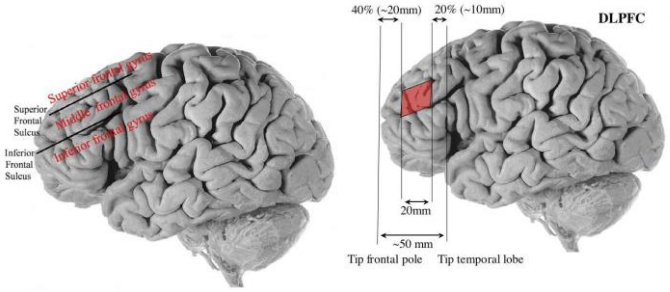

Figure 4.9. DLPFC boundaries in a gross brain dissection.[58]

The ROI's for the ACC and PCC were done in the coronal and sagittal planes and were standardized by the University of North Carolina Neuroimaging Library.[73] The cingulate gyrus is first outlined in the sagittal view to determine boundaries for the inferior and superior boundaries. The inferior border for both the ACC and PCC were the corpus callosum and the superior border was the cingulate sulcus. Then the ACC ROI was continued to be outlined in the coronal plane to determine the inferior, medial and posterior boundaries. The anterior border of the ACC was determined to be at the most rostral slice where a tracing from the sagittal view was present. The medial borders were identified as the inter-hemispheric fissure. The gray matter surrounding the identified gyrus was determined to be the lateral border. The posterior border of the ACC was identified to be at a line drawn from the middle of the mammillary bodies also defined as one slice posterior to the last slice that the inferior portion of the fornix is visible in a sagittal view (Fig. 4.10).

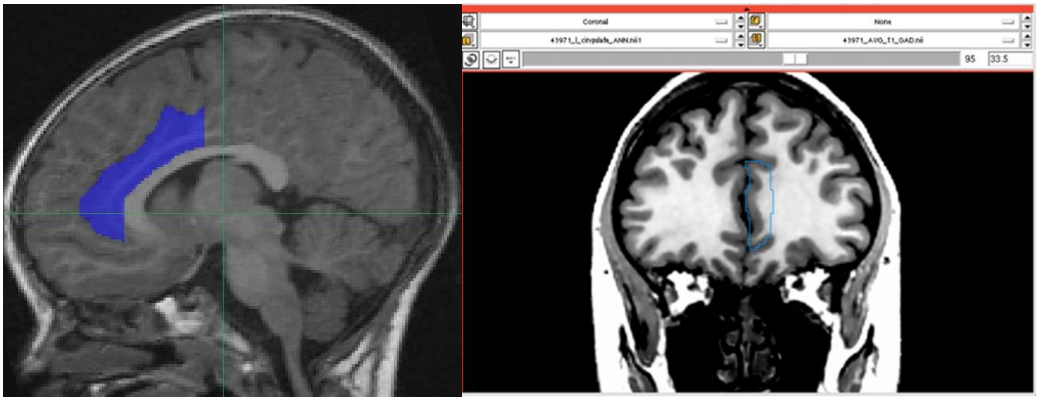

Figure 4.10 Traces of the ACC in the sagittal and coronal views. [59]

The anterior and posterior boundaries of the PCC were drawn in the sagittal plane. The anterior border of the PCC was determined at the posterior boundary of the ACC. And the posterior boundary of the PCC was determined to be the caudal-most point of the splenium of the corpus callosum (Figure 4.11).

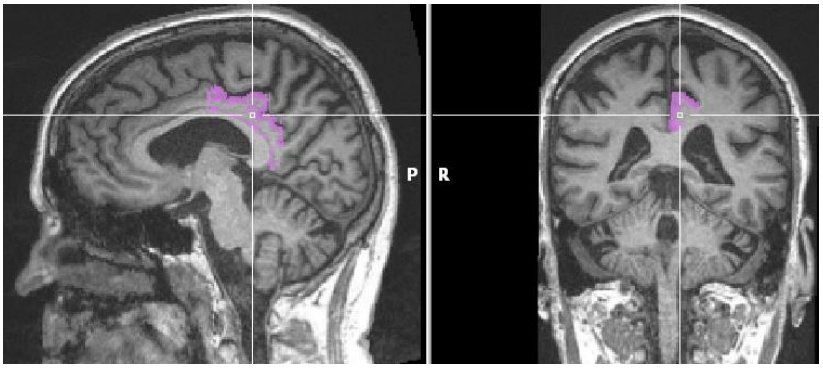

Figure 4.11. Traces of PCC in sagittal and coronal views.

Neuroanatomical guidelines were established for drawing the precuneus area by the UNC Neuroimaging Library and were also done in the coronal plane.[73] The inferior border

was determined to be the deepest point of the posterior occipital sulcus. When the posterior occipital sulcus disappears the inferior border changes to the dorsal bank of the superior parietal sulcus. The superior boundary was determined to be the superior rim of the medial surface of the hemisphere until the end is reached (Fig. 4.12).

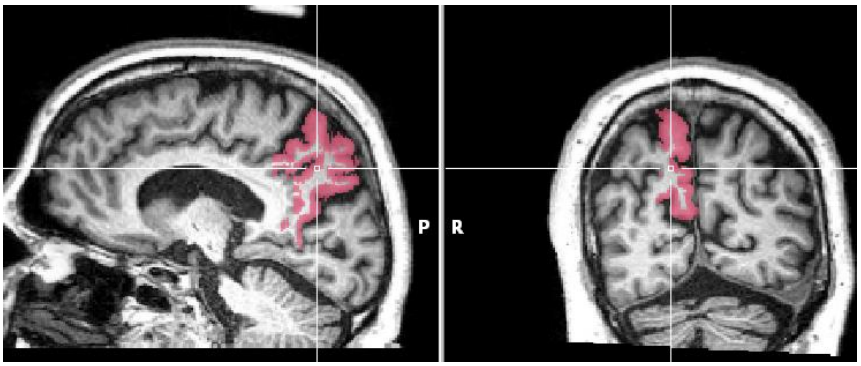

Fig. 4.12. Traces of the precuneus in sagittal and coronal views.

2.3.5 Intervention

An aerobic exercise program based on principles for exercise prescription according to the American College of Sports Medicine (American College of Sports Medicine, 2006) was conducted at the Minneapolis VA Medical Center Fitness Center or Bethesda Rehabilitation Hospital Physical Therapy clinic in St. Paul, MN, in a group format and was led by trained Doctor of Physical Therapy (DPT) students who were supervised by a licensed physical therapist. Each TBI subject participated in the aerobic exercise intervention for 45-60 minutes, 3 times a week for 12 weeks. Attendance, duration, exercise intensity and heart rate prior to, during, and following aerobic exercise session waslogged for each subject visit.

Subjects had the option of performing their program on treadmill, cycle ergometer or upper extremity ergometer as long as they were able to obtain their designated target heart rate for that week. The maximal heart rate (max HR) for each subject was determined through the equation (220 –age) and the target heart rate. The 45-60 minute session included a 5-10 minute warm up at 20-30% of the subject's max HR, an aerobic period of 20-40 minutes, and a 5-10 minute cool down period ramping down to 20-30% of max HR. The ramp and resistance for each device were determined by the MET level corresponding to the subject's target heart rate for the session. The intensity of the aerobic period for each exercise session corresponded to the percentages below:

Aerobic Exercise Protocol

Aerobic phase (15-30 minutes):

Week 1-3: Aerobic exercise will be at least at a light level for 15-20 minutes at 40-50% of maximal heart rate.

Week 4-7: Aerobic exercise will be at least at a moderate level for 20-30 minutes at 50-60% of maximal heart rate.

Week 8-12: Aerobic exercise will be at a high intensity level for 20-30 minutes at 60-80% of maximal heart rate.

If subjects were allowed to progress at a faster rate than the one prescribed above if cardiovascular measures indicated that it was safe to do so.

2.3.6 Data Analysis

fMRI Analysis

Both visual and statistical analyses were used to analyze each subject's individual fMRI changes in volume (voxel count), intensity, and the laterality index during each predictor (0-back, 2 back, -0+2 back), within each designated ROI for this single-subject design. A customary method of data analysis for single-subjects designs is visual analysis. Kazdin defines "visual analysis" as reaching a judgment about the reliability or consistency of intervention effects by visually examining graphed data.[56-57] Phase visual analyses are based on changes in three characteristics of data: level, trend and slope.[55] Level refers to the magnitude of change after the point of intervention or value of the behavior at the last data point of one phase compared with the next adjacent phase. Trend refers to the direction of the change within a phase and can be described as stable or variable and slope refers to the angle or rate of change during a trend.[55] Slope refers to the magnitude of the target behavior over time.[55]

A split middle technique entails drawing a median line for the posttest data was used to enhance the reliability of the visual analysis. This technique results in a celeration line which represents the linear trend and slope for the posttest data points.[55] This type of analysis allows the opportunity to explore inter-subject and intra-subject variability and closely view patient behaviors and responses that are often indiscernible using traditional experimental statistics.[56, 57]

The single-subject statistical analysis used in this study was the two-standard deviation

bandwidth method. Statisical analysis included graphing the pretest and posttest data points. It is recommended to have a minimum of three data points in each phase for single-subject design.[55] In single-subject research a baseline phase occurs when no intervention is given. In this study, a series of three baseline tests was performed over the course of one week to achieve a relatively stable baseline. Then, the mean and standard deviation of the data points for the pretest baseline data were calculated. Next, bands were drawn on a graph corresponding to ± 2 standard deviations above and below the mean extending into the posttest phase. Significance was determined if two consecutive posttest data points fell outside the two standard deviation bandwidth.[55] This statistical significance is based on the assumption that the likelihood of such an event occurring is less that 5 out of 100.[75] An example of the graphing method is presented in Figure 4.13.

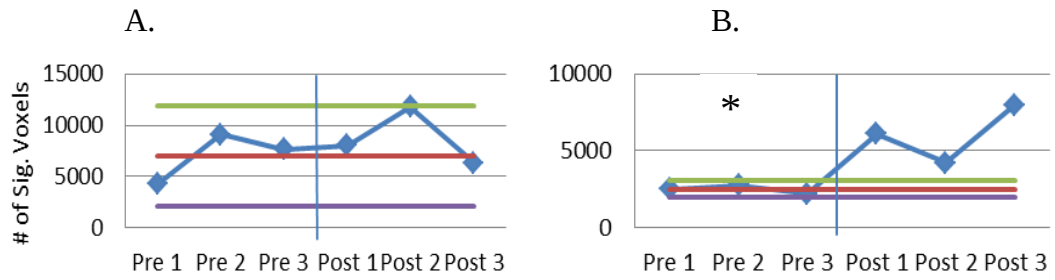

Figure 4.13. Example of the two standard deviation bandwidth method of graphing and analysis. Significance was determined if two consecutive posttest data points fell outside the two standard deviation bandwidth. Red line signifies the pretest mean, green line indicates the upper limits of 2 standard deviations and the purple line indicates the lower limit of 2 standard deviations. Vertical line indicates the timing of the exercise intervention. A. Graph showing an insignificant result. B. Graph showing a significant result.

Aerobic Capacity Analysis

This secondary measure ensured that the subjects improved their aerobic capacity

following the 12-week exercise intervention, the dependent variable of VO_2 max was analyzed from pretest to posttest. Since there was only one measurement of this variable pretest and posttest and due to the finding that the data was not normally distributed, a nonparametric Wilcoxon Signed-Ranks test was used to determine statistically significant change. The non-parametric Wilcoxon Signed-Ranks test is analogous to the parametric paired t-test and can be appropriately used to conduct a comparison of two related samples or repeated measurements when the dependent variable is not normally distributed.[55] Significance was set at an alpha level of $P < .05$.

Working Memory Task Analyses

In order to study whether subjects improved their working memory following participation in the aerobic exercise intervention, subjects performed two separate N-back tasks (0 back and 2 back) and their reaction time and accuracy of the tasks was measured. Due to the skewed nature of the reaction times, the logarithm of the reaction times was used for the statistical analysis. The relationship between logarithm of the reaction time, aerobic intervention, and memory task was modeled with a mixed model with both fixed and random effects. The mixed model for the logarithm of reaction time accounted for the fixed effects including intervention, two tasks (0-back and 2-back), six blocks (1-6), and three MRIs (1,2,3) for each of the seven subjects in the study. The subjects represented the random effect. Six blocks of fifteen 0 back and fifteen 2 back reaction time and accuracy measurements were recorded for each subject, during each of the three fMRI testing periods both pre- and post-intervention.

A similar model was fit to study the accuracy of the subjects performing the same tasks pre- and post-intervention. Since the accuracy was recorded as a binary of whether the subject answered correct or incorrect, a generalized mixed model was used. The logit link function was used to relate the number of correct answers to the fixed and random effects. The same dependent variables that were used to model the reaction time were to model the accuracy. Analysis was performed using software from SAS Institute Inc. (SAS/STAT ®9.2, Cary, NC: SAS Institute Inc. 2009).

Table 4.4. Mixed Model for N-back Accuracy and Reaction Time Analysis

Mixed Model Fixed Effects		
Effect	**Levels**	**Values**
Subjects	7	1, 2,3,4,5,6,7
Intervention	2	Post, Pre
Task	2	0-back, 2-back
fMRI	3	1, 2, 3
Block	6	1, 2, 3, 4, 5, 6

4.5. Results

4.3.1. fMRI Results

Voxel Count Index

Hypothesis 1 $_{B.1)}$ called for a decrease in the TBI subject's voxel count index within the DLPFC and precuneus during the more difficult 2 back task following participation in the 12-week aerobic exercise intervention. Hypothesis 2 $_{B.1)}$ called for a decrease in the voxel

count of the ACC and the PCC during both the 0 back and 2 back tasks following participation in the exercise intervention. Analysis of the voxel count in each ROI using the two standard deviation bandwidth method showed mixed results in each of the subjects. Complete graph findings for each subject for the DLFPC are available in Appendix 1, graph findings for the precuneus are available in Appendix 2, graph findings for each subject for the ACC are available in Appendix 3, and graph findings for the PCC are available in Appendix 4.

0 Back Task

Results for the DLPFC for each predictor condition were mixed. A visual assessment of the direction of the trends for the DLPFC of the graphed data shows that one subject trended toward an increase and three subjects demonstrated a significant increase in the number of significant voxels in the right DLPFC during the 0 back task following the aerobic exercise intervention. Significant findings are reported for the 0 back task in Figure 4.1A. In the left precuneus, one subject demonstrated a significant increase and two subjects a significant decrease with no noticeable directions in trend for the other subjects. In the left PCC, two subjects demonstrated an increase and one a decrease with no marked directions in trend in the other subjects. In the ACC, there was no discernable change.

2 Back Task

A visual assessment of the direction of the trends for the DLPFC of the graphed data

shows that with the exception of two subjects (Subject 5 and 7), lines were either significant or trended toward an increase in the volume on the left side during the 2 back task. Significant findings are reported for the 2 back task compared to rest (2 back) in Figure 4.1 B. Two subjects demonstrated a significant increase on the right side and two subjects demonstrated a significant or trend toward a decrease in the number of voxels in the DLPFC bilaterally following the aerobic exercise intervention.

In the precuneus, three subjects demonstrated a significant decrease on the left side and two on the right side. In the visual analysis, five out of the seven subjects appear to be trending downwards in the precuneus bilaterally. In the PCC, although one subject shows a significant decrease bilaterally, the other subjects' lines appear to be stable. In the ACC, the rostral ACC appears to be trending downward with one subject being significant and the caudal ACC appears to be trending upward with one subject being significant. Also interesting to note is the differences between the subjects themselves. Subjects 2 and 6 seem to display a significant increase in most ROIs overall, while Subjects 5 and 7 show an overall trend of decreasing their volume of activation.

-0+2 Back Task

During visual analysis of the -0+2 back task comparison, the lines trended toward an increase the volume in the bilateral DLPFC voxel count in 3 subjects. Two additional subjects showed a significant increase in the right DLPFC while Subject 5 showed a significant decrease on the right side. Significant statistical findings are reported for the

2 back task without the voxels activated during the -0+2 back in Figure 4.1 C. In the precuneus, four out of the seven subjects demonstrated either significant increases or decreases in the number of significant voxels. In the PCC, both the statistical and visual analysis are mixed with Subject 5 showing a significant decrease bilaterally and subject 6 showing an increase bilaterally. Three subjects also showed a significant change in the caudal ACC bilaterally. Two demonstrated an increase and one a decrease. Again as in the 2 back analysis above, Subjects 2 and 6 seem to display a significant increase in most ROI's overall, while subjects 5 and 7 show an overall trend of decreasing their volume of activation.

A.

0 back	Subj	DLPFC		Precun		PCC		ACC	
		L	R	L	R	L	R	R	C
	1								
	2	↑	↑			↑		↑	
	3		↑	↓					
	4								
	5		↓	↓		↓			
	6			↑		↑			
	7		↑						

B.

2 back	Subj	DLPFC		Precun		PCC		ACC	
		L	R	L	R	L	R	R	C
	1			↓					
	2	↑							
	3		↑						↑
	4								
	5	↓		↓	↓	↓	↓		
	6		↑					↓	
	7		↓	↓	↓				

C..

-0+2 back	Subj	DLPFC		Precun		PCC		ACC	
		L	R	L	R	L	R	R	C
	1								↑
	2	↑	↑	↑				↑	↑
	3								
	4								
	5		↓	↓		↓	↓		↓
	6		↑	↑	↑	↑	↑		
	7			↓	↓				

Figure 4.14. Significant voxel count changes for each subject during each predictor task comparison for each ROI following the 12-week exercise intervention. A. 0-back compared to rest (0 back). B. 2 back compared to rest (2 back). C. 2 back task compared to 0-back (-0+2 back).

Intensity

Hypothesis 1 $_{B.1)}$ called for a decrease in the TBI subject's intensity of activation within

the DLPFC and precuneus during the 2 back task following the exercise intervention. Hypothesis 2 $_{B.1)}$ called for a decrease in the intensity of activation in the ACC and PCC in both the 0 back and the 2 back following participation in the exercise intervention. Analysis of the intensity changes in each ROI using the two standard deviation bandwidth method also showed varied results. Complete graph findings for each subject for the DLFPC are available in Appendix 5, graph findings for the precuneus are available in Appendix 6, graph findings for each subject for the ACC are available in Appendix 7, and graph findings for the PCC are available in Appendix 8.

0 Back Task

Significant findings are reported for the 0 back task in Figure 4.15 A. During the 0 back task compared to rest (0 back), only one subject demonstrated a significant increase on the left side (Subject 5) and the visual analysis yielded no trends in the other subjects. In the precuneus, overall the visual analysis showed a trend toward increasing signal intensity bilaterally for all subjects except for Subject 4 who demonstrated a statistically significant increase in intensity. Three subjects of the above subjects demonstrated a statistically significant increase in precuneus intensity. In the PCC, the findings are dramatically mixed. The visual analysis did not demonstrate any clear trends and are split with half of the subjects increasing and half decreasing. Within those findings, two subjects demonstrated a clearly significant increase and one subject a significant decrease. In the ACC there was minimal overall change.

2 Back Task

Significant findings are reported for the 2 back task compared to rest (2 back) in Figure 4.15 B. Visual analysis for the DLPFC are mixed and unremarkable. In the precuneus, three subjects demonstrated a significant increase in the right precuneus and two subjects on the left. Except for two subjects (Subject 4 and 7), overall visual analysis shows a trend toward increasing intensity in the precuneus. In the PCC, three subjects show a significant increase in the intensity of activity bilaterally with the visual analysis yielding no further findings. In the ACC, there is only one subject with a significant increase in the caudal area and no visible trend in the rest of the subjects.

-0+2 Back Task

Significant findings are reported for the 2 back task without the voxels activated during the 0 back task (-0+2 back) in Figure 4.15 C. In the DLPFC, Subject 2 shows an overall significant increase bilaterally, and Subjects 5 and 7 a decrease bilaterally with a dramatic change in level. Visual analysis demonstrates no apparent trends in any other subjects. In the precuneus, again two subjects (Subjects 1 and 6) show significant changes in both the negative and positive directions respectively. Visual results from the other subjects are unremarkable. In the PCC, two subjects demonstrate significant increases in intensity with a marked change in level. In the visual analysis five of the subjects clearly demonstrate a trend toward an increase in PCC intensity bilaterally. In the ACC, results are mixed with 2 subjects significantly increasing activity on both the rostral and caudal areas and one subject significantly decreasing intensity caudally. In the visual analysis,

again, the results are variable with the remaining subjects.

A.

0 back

Subj	DLPFC		Precun		PCC		ACC	
	L	R	L	R	L	R	R	C
1				↑				
2					↑			
3			↑	↑			↓	↑
4				↓	↓			
5	↑				↑	↑		
6				↑				
7								

B.

2 back

Subj	DLPFC		Precun		PCC		ACC	
	L	R	L	R	L	R	R	C
1	↑			↑				
2					↑	↑		
3	↑		↑	↑	↑	↑		↑
4			↓					
5				↑	↑	↑		
6			↑					
7								↑

C.

-0+2 back

Subj	DLPFC		Precun		PCC		ACC	
	L	R	L	R	L	R	R	C
1				↓				
2		↑					↑	
3						↑		
4								↓
5	↓	↓			↑	↑		
6			↑				↑	
7	↓							

Figure 4.14. Significant intensity changes for each subject during each predictor task comparison for each ROI following the 12-week exercise intervention. A. 0-back compared to rest (0 back). B. 2 back compared to rest (2 back). C. 2 back task compared to 0-back (-0+2 back).

Laterality

Hypothesis 3. $_{B.1)}$ called for a more positive laterality index indicating greater left hemispheric involvement during the N-back task following participation in a 12-week aerobic exercise intervention. Analysis of the change in laterality index or change in the volume of hemisphere activation in each ROI using the two standard deviation bandwidth method revealed mixed results. The laterality index (LI) [(Volume left – Volume right)/ (Volume left + Volume right)] was determined and was graphed for each ROI and each

Task (0 back, 2 back, -0+2 back) for each subject (Appendix 3). A LI of +1.0 indicates Complete left hemisphere activation, a value of 0 indicates equal activation between hemispheres, and a value of -1.0 indicates complete right hemisphere activation. There were no significant changes in the volume of hemispheric activation during the 0 back task in any of the ROI's. During the 2 back task in the precuneus, two subjects demonstrated a significant change in the laterality index from the left to the right in the precuneus. And another subject exhibited a similar significant change in the volume of activation from the left to the right during the -0+2 back task (Figure 4.15).

2 back

Subj	DLPFC		Precun		PCC		ACC	
	L	R	L	R	L	R	R	C
1								
2				X				
3								
4								
5				X				
6								
7								

Figure 4.16. Significant changes in the laterality index (LI) for each subject and ROI during the predictor tasks: A. 2 back compared to rest (2 back). B. 2 back task compared to 0-back (-0+2 back). X denotes the change in the volume of hemispheric activation.

3.2 Aerobic Capacity Results

Hypothesis 1. (B.2) required a comparison of the change in the TBI subjects' pre-exercise and post-exercise VO_2 max during a graded treadmill test to measure the maximal oxygen uptake. The ratio scale data for this test were not normally distributed. Therefore, the non-parametric Wilcoxon Sign-Ranks test was utilized. Wilcoxon Sign-Ranks test results indicated that following participation in 12-weeks of aerobic exercise, there was a significant improvement in the subjects' VO_2 max (Z= 14), (P = .016). All

seven subjects demonstrated improved cardiovascular fitness following participation in the 12-week aerobic exercise program with a mean improvement of 4.2 ml/kg/min. No adverse events were reported during the maximal treadmill testing or during any of the training sessions. Subject compliance with the exercise intervention is shown in Table 4.5. Mean compliance was 84%. It is also important to distinguish that Subject 4 and 5 had markedly decreased compliance compared to their counterparts (42 an 64% respectively).

Table 4.5. Intervention compliance.

Subject	Number of visits	% Compliance	Exercise device
1	36	100%	Treadmill & Bike
2	36	100%	Treadmill
3	35	97%	Treadmill
4	15	42%	Bike
5	23	64%	Treadmill
6	32	89%	Treadmill & Elliptical
7	35	97%	Bike

3.3. Working Memory Results

Hypothesis 1.$_{(B.3)}$ required a decrease in the TBI subjects' pre-exercise and post-exercise reaction time during the 0 back and 2 back tasks following participation in a 12-week aerobic exercise intervention. Based on previous literature regarding the beneficial effects of aerobic exercise on working memory, it was hypothesized that following the intervention subjects would demonstrate a decrease in reaction time signifying an improved speed of processing. The relationship between reaction time, aerobic

intervention, and memory task was modeled using a multiple linear regression (MLR) model with both fixed and random effects. The mixed MLR model on the log reaction time accounted for the fixed effects including intervention, two tasks, six blocks (1-6), and three MRIs (1,2,3) for each of the seven subjects in the study. The subjects represented the random effect. Fifteen 0 back and fifteen 2 back reaction time and accuracy measurements were recorded for each subject, for 6 blocks, for each of the three fMRI testing periods at both pre- and post-intervention. Reaction time demonstrated a significant decrease following the aerobic exercise intervention (t=-2.61, $P<.009$) (Appendix 12). The parameter of the block order of the 0 back or 2 back task was also significant for the first block (t=-2.36, $P=.018$), showing a lower reaction time for the first blocks of the N-back tasks.

Hypothesis 2.$_{(B.3)}$ required an increase in the TBI subjects' pre-exercise and post-exercise accuracy during the 0 back and 2 back tasks following participation in a 12-week aerobic exercise intervention. Based on previous literature regarding the beneficial effects of aerobic exercise on working memory, it was hypothesized that following the intervention subjects would demonstrate an increase in task accuracy. A similar model was fit to study the accuracy of the subjects performing the same tasks pre- and post-intervention. Since the accuracy was recorded as a binary of whether the subject answered correct or incorrect, a generalized, mixed MLR was used. The generalized, mixed MLR model with the logit link function was used to model the number of correct answers. The same fixed and random effects were used to study the accuracy as were

used to study the log reaction time. Accuracy for the group of seven subjects for each of the seven subjects in the study demonstrated a significant improvement following the exercise intervention (t=5.66, $P<.001$) (Appendix 13). Covariates of intervention, two tasks, six blocks (1-6), and three MRIs (1,2,3) were taken into account during the analysis. The parameter of the block order of the 0 back or 2 back task was also significant for the first and second block (t=-3.97, $P< .0001$) and (t=-2.07, $P=.04$) respectively showing a lower accuracy for the first two blocks of the N-back tasks.

4.5. Discussion

To the best of my knowledge, the current study represents the first effort to examine the effect of aerobic exercise on BOLD signal changes following TBI. TBI patients are particularly impaired in working memory and provide a unique opportunity to study the neural basis of aerobic exercise as an intervention to improve cognition in an impaired population. These deficits arise in part from diffuse axonal injury (DAI) which disconnect brain regions.

4.5.1 Change in Aerobic Capacity

The baseline VO_2 measurements of the subjects in this study are comparable with those in other studies and further illustrate the poor aerobic capacity of people in the chronic phase of TBI. The importance of maintaining healthy cardiovascular fitness is important for both neurologically intact as well as TBI and other neurologically impaired populations. As hypothesized, in the group analysis, the subjects significantly improved

their aerobic capacity as measured by the change in VO_2 max following the 12-week aerobic exercise intervention (P = .016). The results of this study agree with those that have investigated the response of other TBI subjects to aerobic exercise. It is also important to note that despite subject's memory and the inherent unreliability of the TBI population, the mean compliance during the 12-week exercise intervention was at 84%, which is approximately 20-35% higher than exercise compliance averages in other impaired populations like diabetes, or CVA (50-65%).[76,77]

4.5.2. Change in Working Memory

As anticipated, subjects demonstrated improved working memory as shown in both a decrease in reaction time (P<.009) and an increase in accuracy (P<.001*)* following participation in aerobic exercise. It is a well-established finding that animals housed with access to a running wheel demonstrate improved memory compared to their sedentary counterparts.[78-82] This outcome was maintained in a brain injured rodent population as long as the exercise occurred in the chronic phase of their recovery.[83-85] In a study of 124 healthy elderly, randomized to either a 10 week walking group or a toning/control group, Kramer et al (1999) showed significant improvement in the executive control processes of planning, scheduling, inhibition, and working memory.[86]

Findings from the working memory results also demonstrated that the block order was also a significant contributing factor within the model for both reaction time (P=.018) and accuracy (P< .0001). Results show that subjects were less likely to perform accurately and more likely to have a higher reaction time in the later blocks than in the

first or second block of the N-back tasks, potentially showing that task fatigue may have been a factor in the outcomes.

These data extend the current knowledge base by demonstrating improvements in working memory following participation in an aerobic exercise intervention and goes one step further by demonstrating these effects in a human TBI group.

4.5.3. Change in fMRI Brain Activity

Change in Dorsolateral Prefrontal Cortex (DLPFC) Activity

A predominantly right-sided frontoparietal network is engaged during attentionally demanding tasks. Damage to these regions can lead to impairments of attention and working memory.[87] In the literature, it has been well documented that the DLPFC is an important part of the frontoparietal network and is thought to facilitate "executive" functions such as updating, monitoring, and manipulating new information.[87-89] Recent literature has also shown that laterality in the DLPFC matters. Healthy adults show sustained increases in right DLPFC activation in response to increasing task load.[87] Moreover, decreased activation on the right DLPFC has been observed in healthy adults acclimating to task demands over repeated trials.[89]

When considering cases of brain trauma, McAllister et al. (1999) were the first to use fMRI to examine working memory deficits in individuals with mild TBI.[46] When comparing healthy adults to individuals with mild TBI on the N-back task, examiners observed increased right DLPFC activation in individuals with mild TBI during higher

versus lower working memory load conditions. In the first fMRI examination of individuals with moderate-to -severe brain trauma, Christodoulou et al. (2001) noted increased right DLPFC recruitment on a paced auditory serial addition task (PASAT), a task requiring significant processing speed and WM demand.[48] In a more recent study by Medaglia et. al (2012,) fMRI again demonstrated an increase in right DLPFC activity but with a reduction in that activation following task practice following with moderate-to–severe TBI.[90]

What remains undetermined in the literature is the role that the increase in right DLPFC recruitment plays following TBI. Current theories include that of brain reorganization, in which the additional DLPFC recruitment reflects an underlying neural change.[90] In the absence of this change, performance deficits would appear. The second theory is that of compensation. Neural compensation is similar to the brain reorganization theory, but does not believe that neural changes or plasticity occur. This theory maintains that the additional recruitment is necessary for sustained task performance.[91-93] Finally the third explanation surmises that the increase in right DLPFC recruitment may more likely be recruited due to the limited resources of a "challenged" neural system.[90,94-95] This explanation would infer that the increase in right DLPFC activity following TBI is similar to the changes seen in healthy adults with increased working memory load. But following TBI, the increase in DLPFC activity becomes evident at lower thresholds.

Although there were significant changes in DLPFC following exercise in some of the

subjects, in this study, the findings are mixed for each predictor comparison. However, with the use of a single-subject design, it is possible to delve more deeply into the individual characteristics of each subject to look for commonalities. Given the findings from the literature above, the hypothesized change of a decrease in the right DLPFC or an increase in activity in the left DLPFC was not apparent in all cases with moderate-to–severe TBI. However, this did occur for Subject's 5 and Subject 7 for both intensity and voxels with the more difficult 2 back task in comparison to rest and the 2 back task in comparison to the 0 back task (-0+2) following participation in the exercise intervention. These results are similar to those found following task practice, suggesting a consolidation of activity and improved neural efficiency._ The interesting difference in regards to both of these subjects is that they exhibited the longest post-injury times (30 and 23 years respectively). For Subject 2 who was at an intermediate time since injury (seven year), a significant increase in the left DLPFC was noted in the voxel count during the 2 back compared with rest, and a significant increase bilaterally in both voxel count and intensity during the -0+2 comparison. For the subjects whose injuries were more recent, especially Subjects 3 and 6 (who were near only 1 post injury, both exhibited sharp increases in both their voxel counts and intensity in the right DLPFC following the exercise intervention.

The preponderance of increased activity for four of the subjects in the right DLPFC during the 0 back task is the opposite of the hypothesis and more difficult to explain. It is possible that the exercise intervention exacerbated the already overactive right DLPFC

but this does not correspond to the lack of any decrement in the 0 back accuracy or reaction times.

Also interesting are the laterality index changes which represent hemispheric dominance for each subject (Appendix 3). During the -0+2 back task comparison, the majority of subjects (5 out of 7) demonstrated an overall trend toward increasing the dominance of the left hemisphere following the exercise intervention. It has been proposed that the right hemisphere is differentially recruited in TBI due to the role it plays in handling novel task demands. In neurologically intact subjects, early in a new task the right hemisphere is preferentially dominant early in a new task. But when a plan for the task is formalized, there is a rapid leftward shift in resources. A possible explanation for the trend toward the subjects' leftward shift following the aerobic exercise intervention may be that they were more efficiently able to organize their cognitive resources to perform the task.

Despite variations, the findings in the DLPFC following the aerobic exercise intervention are interesting. Given the early state of the research and the diverse theories regarding why TBI activation tends to be greater and more right side dominant during working memory tasks, it is possible that the mechanism of recovery is more complex than originally believed. It also opens the possibility that cortical change as a result of an intervention may be individualized depending on the time since injury or the particular deficits of the patient.

Change in Precuneus Activity

Another important component of the frontoparietal task positive network that has been shown to regulate attention, processing efficiency and working memory is the precuneus cortex. The precuneus has demonstrated strong network connections with the DLPFC.[26-31] Interestingly, research has revealed a greater influence of the parietal on the frontoparietal network during challenging tasks in healthy controls compared to TBI subjects.[94] And as the task increased in difficulty, healthy subjects exhibited an anterior (DLPFC) to posterior (precuneus) shift.[94] It has also been found that with practice, both healthy and TBI subjects showed an increase in this anterior posterior shift.[94] The meaning of these changes is yet unclear due to the early state of the literature.

In this study, the most marked change in the precuneus occurred in the 2 back comparison. Six subjects demonstrated either significant or an increased trend toward increased precuneus intensity with a decrease in the number of activated voxels. This decrease in volume combined with increased intensity is a pattern that is closer to normal activation with a more intense and less dispersed area of activation for the 2 back task.[48] The shift may also reflect a decrease in the attentional resources required from the prefrontal cortex resulting in focusing on the representation of the task.[90] Subject 4 was the lone participant that demonstrated minimal change in intensity for the 2 back task. It is noteworthy that Subject 4 also had the lowest compliance percentage with the exercise intervention. The change in the laterality indices (either significant (2 subjects) or trend (3 subjects) from the left toward the right in both the 2 back and -0+2 back tasks was also

observed. So it appears that the shift following the aerobic exercise intervention moved posteriorly and to the right. Again, as with the DLPFC, it is yet unclear due to current literature whether this shift is reflects an underlying neural change, neural compensation, or whether the right side is more likely be recruited due to the limited resources of a "challenged" neural system. Given the more consistent group findings with the 2 back and -0+2 back comparisons, it seems that individual characteristics play less of a role in the precuneus activation changes following exercise.

Change in Anterior Cingulate Cortex (ACC) Activity

The ACC can be divided anatomically based on emotional (rostral) and cognitive (caudal) components. The rostral part of the ACC is connected with amygdala, hypothalamus, and anterior insula, and is involved in emotion and motivation. In contrast, the caudal part of the ACC is connected with the prefrontal and parietal cortices making it a central area for processing top-down and bottom-up stimuli. It has also been suggested increases in caudal ACC activity occur in response to the generation of behavioral adaptations following errors in performance.

Within the context of this study changes in the ACC were variable. However, one surprising finding is that during the 2 back task the subjects most impaired (Subjects 3 and 7), demonstrated significant increases in caudal ACC intensity following the aerobic exercise intervention. Based on the varied findings and limited subjects in the study, it is difficult to determine an overall trend to make any inferences.

Change in Posterior Cingulate Cortex (PCC) Activity

The PCC is a highly connected and highly metabolically active brain region that has been shown to have a common pattern of rapid deactivation during attentionally demanding tasks. This makes the PCC an important component of the Default Mode Network (DMN). The PCC has been shown to have increased activity during the retrieval of autobiographical memories, planning for the future, as well as during unconstrained "rest" when the brain is thought to be "daydreaming".[7] It is also thought to potentially play a role in controlling the balance between internally and externally directed thoughts.[8]

Literature has consistently demonstrated abnormalities in the PCC following TBI. Studies have shown a distinct more extended increase in the PCC which correlated to decrements in performance during an attentionally demanding task.[47] The increased activation of the PCC has been linked to "mind wandering", distractibility and mental fatigue.[54] Patients with TBI also have difficulty switching from relatively automatic to controlled responses, often resulting in perseverative behavior which has been shown to be associated with failure of task dependent deactivation of the PCC.[38] Diffuse axonal injury is associated with reduced metabolism in the PCC and the damage to the structural connectivity is thought to underlie the dysregulation of the DMN following TBI.

Unexpectedly in this study, following the aerobic exercise intervention there seemed to be a an overall trend toward increasing PCC voxel count and intensity for all task

conditions except in Subjects 4 and 5 who were the least compliant with the exercise intervention. Whether this means a decline for the subjects who demonstrated increased PCC activity is unclear, since these subjects' 0 back and 2 back accuracy and reaction time scores did not significantly worsen following the intervention. Another possibility relates to the overlap between brain regions involved in self-processing and regions that constitute the DMN. Using self –talk as a strategy, the subject's thinking about their own performance may explain an increase in PCC activity.[54] The PCC is also implicated in having a role in regulating global brain dynamics due to its high degree of connectivity.[7] Another theory to explain the increase in PCC activity following exercise may be that it is reflective or counterbalancing changes in other brain areas. Another possibility may be that there is an undetermined meaning for this neural change which has yet to be explored.

4.5.4. Study Limitations

One primary limitation of this exploratory clinical study was the challenge of recruiting subjects thereby imposing the absence of a control group. The unpredictability of the TBI population, intensity of the program (3 times each week for 12 weeks), and the requirement that subjects come to an urban medical center for the intervention may have contributed to recruitment difficulties. The demands of traditional experimental methods can become barriers to rehabilitation and brain research in clinical populations, including TBI. However, the exploration of inter-subject and intra-subject variability as well as the ability to evaluate interventions in a small group of subjects is an advantage of single-

subject designs when studying TBI rehabilitation and brain research.[75] Limitations to single-subject designs include limited generalizability due to subject selection and internal validity threats from repeated testing and regression toward the mean. Internal validity may possibly have been impacted by the absence of a follow-up re-evaluation. All subjects knew they were being studied and received the same exercise intervention, potentially resulting in a Hawthorne effect which is the tendency for subjects to perform better when they know they are expected to do so.

Maturation, or the general passing of time was also a potential danger to internal validity of this study. This problem was addressed by having multiple baseline fMRI testing to establish a stable baseline of activation. Research has shown that most cognitive changes occur following TBI occur in the first year. To compensate for this threat the inclusion criteria required subjects to be at least one year post injury. Also it is important to note that the mean time since the subjects' injury was 11.29 years, thereby limiting the potential for spontaneous cognitive recovery. Due to these limitations, investigators must be guarded in stating conclusions and consumers of research must be cautious in their interpretation.

4.5.5. Possible Mechanisms and Future Directions

This preliminary clinical study is the first to investigate the effects of an aerobic exercise intervention on brain activity following TBI. This study does provide evidence for neurophysiologic mechanisms that may underlie changes in brain activity following

exercise. Evidence available in the literature suggests that aerobic exercise may improve brain function through increases in blood flow and actual growth of new blood vessels (angiogenesis) especially in areas related to cognition such as the prefrontal cortex and hippocampus.[96-100]

Aerobic exercise has also been shown to increase in brain catecholamines, particularly dopamine and noradrenalin.[101] Studies show that chronic wheel running in animals increases in noradrenalin and dopamine in several brain regions related to cognition, as well as regulating synaptic plasticity and enhancing neuronal survival and promoting neural repair. They have also been implicated in the up regulation of BDNF (brain derived neurotrophic factor).[89,103]

BDNF has been shown to improve neuronal survival and drive both neuro and synaptogenesis. [102-106] These changes in neuro and synaptogenesis have both been linked to specific areas of the brain related to cognition and also have been found to correlate with behavioral improvement in memory in animal populations.[104,106] In animals, these physiologic changes have been shown to create a foundation for better memory, learning and overall cognitive performance.

These changes have also been found to occur in animal populations following TBI. A study by Griesbach et al. (2004) found exercise increased animal memory on the Morris

Water Maze, as well as up regulating BDNF compared to sedentary animals.[83] In a more recent study by Griesbach, results determined that BDNF counteracted the cognitive deficits associated with the injury and provided evidence that BDNF indeed has a major role in exercise's cognitive effects in the traumatically injured brain.[84] Therefore, it is possible that the underlying mechanisms of increased vascularization, increased neurotransmitters and increased BDNF found following exercise could potentially act to create an enriched environment within the brain for plasticity to occur.

How then do these fundamental physiologic changes following exercise affect brain activity? In a study by Colcombe an Kramer (2004), results indicated that higher fit and aerobically trained older adults demonstrated greater activation in the DLPFC and parietal cortex with a corresponding decrease in the anterior cingulate, an area associated with behavioral conflict.[107] A similar study with children indicated analogous results.[108] During a more difficult cognitive task, higher fit children demonstrated better accuracy coupled with increased prefrontal and parietal recruitment early in the task with a reduction in activity after practice compared with their less fit counterparts. Both of these studies support and show results similar to those found in this preliminary study of TBI patients. But more needs to be done to further investigate these findings before implementing aerobic exercise as an intervention in a TBI rehabilitation setting.

Therefore, future recommendations include a larger randomized control trial to determine more decisively whether the cortical effects found in animal and healthy adult

populations following exercise also apply to the TBI population. Since DAI is one of the underlying physiologic mechanisms of injury following TBI, it is also recommended that diffuse tensor imaging (DTI) be used to determine whether aerobic exercise effects the connectivity of the task positive and default mode networks as well. And finally, since much of the literature regarding positive cortical change following TBI utilizes task practice as an intervention, a study which includes a condition of aerobic exercise with the addition of cognitive training or task practice would also be recommended to compare with each intervention alone.

4.5.6. Summary

In summary, the findings from this exploratory study indicate that participation in a 12-week aerobic exercise intervention did demonstrate significant changes especially in the DLPFC, precuneus and PCC. This study demonstrated feasibility of a 12-week intervention in people with TBI, the observed safety of the treatment and testing procedures. The cortical changes seen in this pilot study all invite a larger randomized control trial with diffuse tensor imaging and network analyses to further examine the effects of exercise in both the task-positive and default mode networks in the TBI population. A larger experimental study would further assist in determining whether aerobic exercise could be used as an adjunct intervention to improve not only cardiovascular fitness but to promote plasticity changes within the brain itself in chronic TBI patients.

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CHAPTER V.

SUMMARY OF FINDINGS

Summary

In summary, Chapter 2 published in 2010 in the Journal of Head Injury Rehabilitation, gave a review of the literature establishing the positive effects of aerobic exercise on cognition.[1] It also described the potential underlying mechanisms that are thought to drive this change including; increased brain vasculature, neurotransmitters and brain derived neurotrophic factor (BDNF) and their beneficial influence on brain plasticity.

In light of the convincing evidence for the effect of aerobic exercise on cognition in healthy young and older adult populations, a hypothesis was developed to investigate the potential of this intervention for rehabilitation of deficits in memory and executive function following TBI. As previously stated, TBI survivors up to 10 years post-injury still have problems with processing speed, memory and executive function which significantly impact their productivity.[2] To this end, the preliminary experiment described in Chapter III describes the effect of a 12-week aerobic exercise intervention on everyday memory, working memory, executive function and disability. And although there are limitations in the study design which limit the interpretation and generalizability of the findings, it was found that following aerobic exercise moderate-to-severe TBI subjects improved on tests of everyday memory, working memory and aspects of disability.

The findings in Chapter III also raised questions regarding the underlying cortical changes that might underlie these behavioral changes in cognition. To investigate this question, the experiment in Chapter IV hypothesized the potential changes in brain activity that might occur following participation in a 12-week aerobic exercise intervention base on previous literature. A single-subject design was used to analyze data to determine not only statistical significance in a small group of subjects, but to also determine individual characteristics which might lead to improvement and be useful for clinical practice. Within the context of this study, statistically significant differences in brain activity were identified although they did not necessarily correspond to the hypothesized directions of change. However, the N-back working memory tests did again demonstrate that there was a behavioral improvement in working memory following the intervention.

This study is the first to examine the effects of aerobic exercise as an intervention to address the cognitive deficits and brain changes that accompany TBI. The findings though varied do indicate that there is evidence to advance to a larger randomized experimental trial to further examine the potential for aerobic exercise to be used an adjunct intervention in the rehabilitation of cognitive deficits following TBI.

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Appendix 1. Modified Dysken Screening Tool

ASSESSMENT FOR CAPACITY TO PROVIDE INFORMED CONSENT

Section 1:

Is the research study voluntary? YES NO

If you choose not to be in the research study, will this change your regular treatment?

YES NO

Once you begin the research study are you free to stop at any time? YES NO

If you drop out of the research study, will this change your regular care? YES NO

One of the risks of the research study is:

Fatigue

Muscle Soreness

Dizziness

Headache

Claustrophobic

Frustrated/ upset

Section 2:

Is the research study voluntary? YES NO

How long will you be in the exercise group?

- 1 week
- 12-weeks
- 1 year
- 1 day

Will you be paid to be in the study? YES NO

If you drop out of the research study, will this change your regular care? YES NO

How many times each week will you come to exercise?

- Everyday
- Three times a week
- One time a week

Is the research study guaranteed to help you? YES NO

If you choose not to be in the research study, will this change your regular treatment?

YES NO

One of the potential benefits of the research study is:

More energy

Increased strength

Improved heart function

Once you begin the research study are you free to stop at any time? YES NO

_____ _____

Subject's Signature **Date/Time**

(must be a full signature) **(must be dated by the subject)**

_____ _____

Signature of Investigator **Date/Time**

_____ _____

Signature of Person obtaining consent if other than the investigator **Date/Time**

Appendix 2. Rancho Los Amigos Cognitive Scale Revised

Level I - No Response Total Assistance

- **Complete absence of observable change in behavior when presented visual, auditory, tactile, proprioceptive, vestibular or painful stimuli.**

Level II - Generalized Response: Total Assistance

- **Demonstrates generalized reflex response to painful stimuli.**
- **Responds to repeated auditory stimuli with increased or decreased activity.**
- **Responds to external stimuli with physiological changes generalized, gross body movement and/or not purposeful vocalization.**
- **Responses noted above may be same regardless of type and location of stimulation.**
- **Responses may be significantly delayed.**

Level III - Localized Response: Total Assistance

- **Demonstrates withdrawal or vocalization to painful stimuli.**
- **Turns toward or away from auditory stimuli.**
- **Blinks when strong light crosses visual field.**
- **Follows moving object passed within visual field.**
- **Responds to discomfort by pulling tubes or restraints.**
- **Responds inconsistently to simple commands.**
- **Responses directly related to type of stimulus.**
- **May respond to some persons (especially family and friends) but not to others.**

Level IV - Confused/Agitated: Maximal Assistance

- **Alert and in heightened state of activity.**
- **Purposeful attempts to remove restraints or tubes or crawl out of bed.**
- **May perform motor activities such as sitting, reaching and walking but without**

any apparent purpose or upon another's request.

- **Very brief and usually non-purposeful moments of sustained alternatives and divided attention.**
- **Absent short-term memory.**
- **May cry out or scream out of proportion to stimulus even after its removal.**
- **May exhibit aggressive or flight behavior.**
- **Mood may swing from euphoric to hostile with no apparent relationship to environmental events.**
- **Unable to cooperate with treatment efforts.**
- **Verbalizations are frequently incoherent and/or inappropriate to activity or environment.**

Level V - Confused, Inappropriate Non-Agitated: Maximal Assistance

- **Alert, not agitated but may wander randomly or with a vague intention of going home.**
- **May become agitated in response to external stimulation, and/or lack of environmental structure.**
- **Not oriented to person, place or time.**
- **Frequent brief periods, non-purposeful sustained attention.**
- **Severely impaired recent memory, with confusion of past and present in reaction to ongoing activity.**
- **Absent goal directed, problem solving, self-monitoring behavior.**
- **Often demonstrates inappropriate use of objects without external direction.**
- **May be able to perform previously learned tasks when structured and cues provided.**
- **Unable to learn new information.**
- **Able to respond appropriately to simple commands fairly consistently with external structures and cues.**

- **Responses to simple commands without external structure are random and non-purposeful in relation to command.**
- **Able to converse on a social, automatic level for brief periods of time when provided external structure and cues.**
- **Verbalizations about present events become inappropriate and confabulatory when external structure and cues are not provided.**

Level VI - Confused, Appropriate: Moderate Assistance

- **Inconsistently oriented to person, time and place.**
- **Able to attend to highly familiar tasks in non-distracting environment for 30 minutes with moderate redirection.**
- **Remote memory has more depth and detail than recent memory.**
- **Vague recognition of some staff.**
- **Able to use assistive memory aide with maximum assistance.**
- **Emerging awareness of appropriate response to self, family and basic needs.**
- **Moderate assist to problem solve barriers to task completion.**
- **Supervised for old learning (e.g. self care).**
- **Shows carry over for relearned familiar tasks (e.g. self care).**
- **Maximum assistance for new learning with little or nor carry over.**
- **Unaware of impairments, disabilities and safety risks.**
- **Consistently follows simple directions.**
- **Verbal expressions are appropriate in highly familiar and structured situations.**

Level VII - Automatic, Appropriate: Minimal Assistance for Daily Living Skills

- **Consistently oriented to person and place, within highly familiar environments. Moderate assistance for orientation to time.**
- **Able to attend to highly familiar tasks in a non-distraction environment for at least 30 minutes with minimal assist to complete tasks.**

- **Minimal supervision for new learning.**
- **Demonstrates carry over of new learning.**
- **Initiates and carries out steps to complete familiar personal and household routine but has shallow recall of what he/she has been doing.**
- **Able to monitor accuracy and completeness of each step in routine personal and household ADLs and modify plan with minimal assistance.**
- **Superficial awareness of his/her condition but unaware of specific impairments and disabilities and the limits they place on his/her ability to safely, accurately and completely carry out his/her household, community, work and leisure ADLs.**
- **Minimal supervision for safety in routine home and community activities.**
- **Unrealistic planning for the future.**
- **Unable to think about consequences of a decision or action.**
- **Overestimates abilities.**
- **Unaware of others' needs and feelings.**
- **Oppositional/uncooperative.**
- **Unable to recognize inappropriate social interaction behavior.**

Level VIII - Purposeful, Appropriate: Stand-By Assistance

- **Consistently oriented to person, place and time.**
- **Independently attends to and completes familiar tasks for 1 hour in distracting environments.**
- **Able to recall and integrate past and recent events.**
- **Uses assistive memory devices to recall daily schedule, "to do" lists and record critical information for later use with stand-by assistance.**
- **Initiates and carries out steps to complete familiar personal, household, community, work and leisure routines with stand-by assistance and can modify the plan when needed with minimal assistance.**
- **Requires no assistance once new tasks/activities are learned.**

- **Aware of and acknowledges impairments and disabilities when they interfere with task completion but requires stand-by assistance to take appropriate corrective action.**
- **Thinks about consequences of a decision or action with minimal assistance.**
- **Overestimates or underestimates abilities.**
- **Acknowledges others' needs and feelings and responds appropriately with minimal assistance.**
- **Depressed.**
- **Irritable.**
- **Low frustration tolerance/easily angered.**
- **Argumentative.**
- **Self-centered.**
- **Uncharacteristically dependent/independent.**
- **Able to recognize and acknowledge inappropriate social interaction behavior while it is occurring and takes corrective action with minimal assistance.**

Level IX - Purposeful, Appropriate: Stand-By Assistance on Request

- **Independently shifts back and forth between tasks and completes them accurately for at least two consecutive hours.**
- **Uses assistive memory devices to recall daily schedule, "to do" lists and record critical information for later use with assistance when requested.**
- **Initiates and carries out steps to complete familiar personal, household, work and leisure tasks independently and unfamiliar personal, household, work and leisure tasks with assistance when requested.**
- **Aware of and acknowledges impairments and disabilities when they interfere with task completion and takes appropriate corrective action but requires stand-by assist to anticipate a problem before it occurs and take action to avoid it.**
- **Able to think about consequences of decisions or actions with assistance when requested.**
- **Accurately estimates abilities but requires stand-by assistance to adjust to task**

demands.

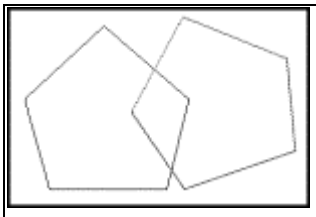
- **Acknowledges others' needs and feelings and responds appropriately with stand-by assistance.**
- **Depression may continue.**
- **May be easily irritable.**
- **May have low frustration tolerance.**
- **Able to self monitor appropriateness of social interaction with stand-by assistance.**

Level X - Purposeful, Appropriate: Modified Independent

- **Able to handle multiple tasks simultaneously in all environments but may require periodic breaks.**
- **Able to independently procure, create and maintain own assistive memory devices.**
- **Independently initiates and carries out steps to complete familiar and unfamiliar personal, household, community, work and leisure tasks but may require more than usual amount of time and/or compensatory strategies to complete them.**
- **Anticipates impact of impairments and disabilities on ability to complete daily living tasks and takes action to avoid problems before they occur but may require more than usual amount of time and/or compensatory strategies.**
- **Able to independently think about consequences of decisions or actions but may require more than usual amount of time and/or compensatory strategies to select the appropriate decision or action.**
- **Accurately estimates abilities and independently adjusts to task demands.**
- **Able to recognize the needs and feelings of others and automatically respond in appropriate manner.**
- **Periodic periods of depression may occur.**
- **Irritability and low frustration tolerance when sick, fatigued and/or under emotional stress.**
- **Social interaction behavior is consistently appropriate.**

Appendix 3. Mini Mental Status Examination (MMSE)

Maximum	Examinations						(1 point per right answer)
Score							ORIENTATION
5							Ask the patient what (year) (season) (date) (day) (month) it is.
5							Ask the patient where he/she is (province) (country) (town or city) (hospital) (floor).
							REGISTRATION
3							Name 3 common objects (e.g., "apple", "table", "penny"). Take 1 second to pronounce each word. Then ask the patient to repeat all 3 words. Give one point for each correct answer. Then repeat them until he/she learns all 3. Make a maximum of 6 trials.
							ATTENTION AND CALCULATION
5							Ask the patient to substract 7 from 100 and keep substracting 7 until you tell him/her to stop. (93, 86, 79, 72, 65) OR Ask him/her to spell "WORLD" backwards. The score is the number of letters in correct order (D_L_R_O_W).
							RECALL
3							Ask the patient for the 3 objects repeated above. Give 1 point for each correct answer. (Note: Recall cannot be tested if all 3 objects were not remembered during registration.)

							LANGUAGE
2							**Show the patient a "pencil" and a "watch" and ask him/her to name them.** **(2 pts)**
1							**Ask your patient to repeat the following:** **« No ifs, ands or buts. »** **(1 pt)**
3							**Ask your patient to follow a 3-stage command:** **« Take a paper in your right hand, fold it in half, and put it on the floor. »** **(3 pts)**
							Ask the patient to read and obey the following :
1							**Close your eyes. (1 pt)**
1							**Write a sentence. (1 pt)**
1							**Copy the following design. (1 pt)**
							
Totals							
Initials							

Appendix 4. Patient Health Questionnaire (PHQ-9)

PATIENT QUESTIONNAIRE PHQ-9

Patient Name: _____**Provider**_____**Date**: _____

1. **Over the last 2 weeks, how often have you been bothered by any of the following problems**?

	Not at all	Several days	More than half the days	Nearly every day
	0	**1**	**2**	**3**
a. Little interest or pleasure in doing things	☐	☐	☐	☐
b. Feeling down, depressed, or hopeless	☐	☐	☐	☐
c. Trouble falling/staying asleep, sleeping too much	☐	☐	☐	☐
d. Feeling tired or having little energy	☐	☐	☐	☐
e. Poor appetite or overeating	☐	☐	☐	☐
f. Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching television.	☐	☐	☐	☐
h. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.	☐	☐	☐	☐
i. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

2. **If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

Not difficult at all	Somewhat Difficult	Very Difficult	Extremely Difficult
☐	☐	☐	☐

3. **If these problems have caused you difficulty, have they caused you difficulty for two years or more?**

_____ **Yes, I have had difficulty with these problems for two years or more.**

_____ **No, I have not had difficulty with these problems for two years or more.**

Number of Symptoms: _____

Total Score for first 9 Questions: _____

Function Score (Question 2): _____

Appendix 5. Alcohol Screening CAGE Assessment

For most people who drink, alcohol is a pleasant addition to eating and to other social activities.
For most adults drinking a moderate amount of alcohol (up to two drinks per day for men, and one drink per day for women and older people) is not harmful. But, many people get into serious trouble because of their drinking.

This short assessment will help you determine if you might have a problem with alcohol. (The name "CAGE" is an acronym formed by taking the first letter of key words from each of the following questions.)

Have you ever felt you should cut down on your drinking?

- **Yes**
- **No**

Have people annoyed you by criticizing your drinking?

- **No**

Have you ever felt bad or guilty about your drinking?

- **No**

Have you ever had a drink first thing in the morning (as an "eye opener") to steady your nerves or get rid of a hangover?

- **No**

Appendix 6. Rivermead Behavioral Memory Test

RBMT–E

Thames Valley Test Company

The Rivermead Behavioural Memory Test – Extended Version

Procedural Guide and Scoring Sheet

Subject and test details

Name

Date of birth

Date of test

Assessment ☐ First ☐ Second

Version ☐ 1 ☐ 2

Note: Before you start the test ensure you have all the appropriate equipment: test materials book and large picture card for Version 1 or 2; timer/alarm; message envelope and book; stopwatch.

1 & 2 First and Second Names

Action: Present three photographic portraits and the first and second names of the people portrayed as described in the test materials.

3 Belongings

Action: Hide two belongings as described in the test materials.

4 Appointments

Action: Demonstrate and set the timer/alarm for about 20 minutes as described in the test materials, and state questions to be asked.

5 Picture Recognition

Action: Present large picture card as described in the test materials.

6 Story (immediate)

Action: Read the story as described in the test materials, and then ask the subject to recall it.

Response: Tick each of the 21 'ideas' correctly or partially recalled.

Correctly recalled ↓ Version 1	Partially recalled (tick) ↓ Version 2
Mr Brian	☐ ☐ Two hundred men
Kelly	☐ ☐ at a shipyard
a Security Express employee	☐ ☐ on Tyneside
was shot dead	☐ ☐ went on strike
on Monday	☐ ☐ this morning.
during a bank raid	☐ ☐ The men walked out
in Brighton.	☐ ☐ over a dispute
The four raiders	☐ ☐ concerning 50
all wore masks	☐ ☐ redundancies.
and one carried	☐ ☐ The shop steward
a sawn-off	☐ ☐ Mr Thomas
shotgun.	☐ ☐ Lindsay
Police detectives	☐ ☐ told reporters
were sifting through	☐ ☐ 'It is outrageous!
eye-witness accounts	☐ ☐ The company has full order books
last night.	☐ ☐ for the next two years.'
A police spokesman said	☐ ☐ A management spokesperson said
'He was a very brave man.	☐ ☐ 'We are hoping to begin
He went for	☐ ☐ fresh negotiations
the armed raider	☐ ☐ at head office
and put up a hell of a fight.'	☐ ☐ tomorrow.'

Raw score

☐ Each 'idea' recalled word-perfect or using a close synonym = 1

☐ Each 'idea' partially recalled or recalled with an approximate synonym = ½

☐ **Total raw score** (max = 21)

Profile score conversion table Profile score = ☐

Predicted (premorbid) intellectual band	Profile score 0	1	2	3	4
Below average	0	1	2–6	7–12	13–21
Average	0–2	3–6	7–11	12–15	16–21
Above average	0–4	5–9	10–13	14–17	18–21

5 Picture Recognition

Action: Present picture cards as described in the test materials.

Response: Record the correct identifications and the number of false positives.

Version 1		Version 2
horse	☐	elephant
clock	☐	wheel
pan	☐	trumpet
racket	☐	motorbike
book	☐	tree
camel	☐	aeroplane
drum	☐	axe
pig	☐	bottle
star	☐	cake
cup	☐	watering can
table	☐	hat
ball	☐	chair
cow	☐	dustbin
kettle	☐	apple
tortoise	☐	pram
rabbit	☐	helicopter
pipe	☐	record player
watch	☐	button
bus	☐	bicycle
bell	☐	cockerel

record false positives here

☐☐☐☐☐ ☐☐☐☐☐

☐☐☐☐☐ ☐☐☐☐☐

Raw score

☐ Each picture correctly identified = 1

☐ Deduct the number of false positives

☐ **Total raw score** (max = 20)

Profile score conversion table Profile score = ☐

	Profile score 0	1	2	3	4
Raw score	0–7	8–11	12–15	16–19	20

7 Face Recognition

Action: Present faces as described in the test materials.

8 Route & 9 Messages (immediate)

Action: Demonstrate the route, leaving message envelope and book at appropriate locations, as described in the test materials. (Adapt the instructions to suit the room if appropriate, and note your route in the column headed 'Your own version' below.)

Response: Record the route taken by the subject and tick message/book boxes as appropriate.

	spontaneously	after prompt
Message picked up	☐	☐
Book picked up	☐	☐

Version 1	Version 2	Your own version	Subject's route
Chair 1	Heater	.....	
Door	Chair 1	.....	
Chair 2	Noticeboard	.....	
Message left at correct location			☐
Window	Table	.....	
Heater	Door	.....	
Table	Chair 2	.....	
Book left at correct location			☐
Noticeboard	Window	.....	

Scoring for Route

Raw score

If the route is completed correctly = 15

If the route is **not** completed correctly calculate the raw score:

☐ 1 Score 1 for each correct location visited regardless of order (max = 7)

☐ 2 Score 1 if the starting place was correct and score 1 if the finishing point was correct (max = 2)

☐ 3 Consider each location in turn together with the location following it, and score 1 if that particular pair order appears somewhere in the correct route list (max = 6)
Note: the last location in the sequence is not counted since there is no location following it.
Note also: If the **same** correct pair order occurs twice (or more) it should only be counted once.

— ☐ 4 Deduct 1 for every incorrect or repeated stage (i.e. a totally different location, or the same location visited more than once)

☐ **Total raw score** (max = 15)

Profile score conversion table Profile score = ☐

Version	Age	Profile score 0	1	2	3	4
1	Below 30 years	0–10	11–12	13	14	15
	30–50 years	0–8	9–11	12–13	14	15
	51 years & over	0–3	4–9	10–13	14	15
2	Below 30 years	0–6	7–10	11–13	14	15
	30–50 years	0–7	8–10	11–13	14	15
	51 years & over	0–4	5–9	10–13	14	15

Scoring for Messages

Raw score

☐ Message picked up spontaneously = 2 / with prompt = 1

☐ Book picked up spontaneously = 2 / with prompt = 1

☐ Message left in correct location = 1

☐ Book left in correct location = 1

☐ **Total raw score** (max = 6)

Profile score conversion table Profile score = ☐

	Profile score 0	1	2	3	4
Raw score	0–2	3	4	5	6

7 Face Recognition

Action: Present face cards as described in the test materials.

Response: Record the correct identifications and the number of false positives.

Version 1		Version 2
p.127	☐	p.127
p.131	☐	p.131
p.137	☐	p.137
p.139	☐	p.139
p.141	☐	p.145
p.147	☐	p.149
p.149	☐	p.155
p.157	☐	p.157
p.159	☐	p.159
p.165	☐	p.165
p.169	☐	p.167
p.171	☐	p.175
p.177	☐	p.177
p.183	☐	p.183
p.185	☐	p.185

record false positives here ☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐

Raw score

☐ Each picture correctly identified = 1

— ☐ Deduct the number of false positives

☐ **Total raw score** (max = 15)

Profile score conversion table Profile score = ☐

	Profile score 0	1	2	3	4
Raw score	0–9	10–11	12–13	14	15

10 Orientation & 11 Date

Action: Ask the 13 questions as described in the test materials.

Response: Record the subject's responses below.

Question/response	Raw score
1 Year 1 point if correct	☐
2 Month 1 point if correct	☐
3 Day 1 point if correct	☐
4 Time 1 point if within half-an-hour of correct time	☐
5 Date 2 points if correct, 1 point if one day out	☐
6 Place 1 point for correct name of hospital or centre, or for number of house **and** street name 0 points for 'a hospital'	☐
7 City/town 1 point if correct (or nearest city/town if necessary)	☐
8 Age 1 point if correct	☐
9 Birth year 1 point if correct	☐
10 Prime Minister/Governor 1 point if first and second names correct ½ point for correct surname only	☐
11 Previous Prime Minister/Governor 1 point if first and second names correct ½ point for correct surname only	☐

12 President

1 point if first and second names correct
½ point for correct surname only

13 Previous President

1 point if first and second names correct
½ point for correct surname only

Total raw score (max = 14)

Profile score conversion table Profile score =

	Profile score				
	0	1	2	3	4
Raw score	0–10	11	12	13	14

4 Appointments

Action: Engage the subject in conversation until the alarm sounds. Prompt the subject for the two questions if not asked spontaneously.

Response

	spontaneously	after prompt
Question 1 asked	☐	☐
Question 2 asked	☐	☐

Raw score

Calculate raw score as follows:

- Each question asked spontaneously = 2
- Each question asked after prompt = 1
- Subject remembers two things had to be done but not what they were = 2
- Subject remembers one thing had to be done but not what it was = 1

Total raw score (max = 4)

Calculate profile score later: add raw score to 'Belongings' score

6 Story (delayed)

Action: Ask the subject to recall the story again as described in the test materials.

Response: Tick each of the 21 'ideas' correctly or partially recalled.

Correctly recalled	Partially recalled (tick)	
Version 1		**Version 2**
Mr Brian	☐	☐ Two hundred men
Kelly	☐	☐ at a shipyard
a Security Express employee	☐	☐ on Tyneside
was shot dead	☐	☐ went on strike
on Monday	☐	☐ this morning.
during a bank raid	☐	☐ The men walked out
in Brighton.	☐	☐ over a dispute
The four raiders	☐	☐ concerning 50
all wore masks	☐	☐ redundancies.
and one carried	☐	☐ The shop steward
a sawn-off	☐	☐ Mr Thomas
shotgun.	☐	☐ Lindsay
Police detectives	☐	☐ told reporters
were sifting through	☐	☐ 'It is outrageous!
eye-witness accounts	☐	☐ The company has full order books
last night.	☐	☐ for the next two years.'
A police spokesman said	☐	☐ A management spokesperson said
'He was a very brave man.	☐	☐ 'We are hoping to begin
He went for	☐	☐ fresh negotiations
the armed raider	☐	☐ at head office
and put up a hell of a fight.'	☐	☐ tomorrow.'

Raw score

☐ Each 'idea' recalled word-perfect or using a close synonym = 1

☐ Each 'idea' partially recalled or recalled with an approximate synonym = ½

— ☐ Subtract 1 point if the subject needed an opening prompt

☐ **Total raw score** (max = 21)

Profile score conversion table Profile score =

Predicted (premorbid) intellectual band	Profile score 0	1	2	3	4
Below average	0	1–2	3–6	7–10	11–21
Average	0–1	2–5	6–10	11–14	15–21
Above average	0–3	4–7	8–12	13–15	16–21

8 Route & 9 Messages (delayed)

Action: Ask the subject to take the route again as described in the test materials. (Adapt the instructions to suit the room if appropriate, and note your route in the column headed 'Your own version' below.)

Response: Record the route taken by the subject and tick message/book boxes as appropriate.

	spontaneously	after prompt
Message picked up	☐	☐
Book picked up	☐	☐

Version 1	Version 2	Your own version	Subject's route
Chair 1	Heater	.....	
Door	Chair 1	.....	
Chair 2	Noticeboard	.....	
Message left at correct location			☐
Window	Table	.....	
Heater	Door	.....	
Table	Chair 2	.....	
Book left at correct location			☐
Noticeboard	Window	.....	

Scoring for Route

Raw score

If the route is completed correctly = 15

If the route is **not** completed correctly calculate the raw score as follows:

☐ 1 Score 1 for each correct location visited regardless of order (max = 7)

☐ 2 Score 1 if the starting place was correct and score 1 if the finishing point was correct (max = 2)

☐ 3 Consider each location in turn together with the location following it, and score 1 if that particular pair order appears somewhere in the correct route list (max = 6)

Note: the last location in the sequence is not counted since there is no location following it.

Note also: If the **same** correct pair order occurs twice (or more) it should only be counted once.

— ☐ 4 Deduct 1 for every incorrect or repeated stage (i.e. a totally different location, or the same location visited more than once)

☐ **Total raw score** (max = 15)

Profile score conversion table Profile score = ☐

Version	Age	Profile score 0	1	2	3	4
1	Below 30 years	0–8	9–11	12–13	14	15
	30–50 years	0–6	7–10	11–13	14	15
	51 years & over	0–6	7–9	10–12	13	14–15
2	Below 30 years	0–3	4–10	11–13	14	15
	30–50 years	0–3	4–9	10–13	14	15
	51 years & over	0–6	7–9	10–11	12–13	14–15

Scoring for Messages

Raw score

☐ Message picked up spontaneously = 2 / with prompt = 1

☐ Book picked up spontaneously = 2 / with prompt = 1

☐ Message left in correct location = 1

☐ Book left in correct location = 1

☐ **Total raw score** (max = 6)

Profile score conversion table Profile score = ☐

	Profile score 0	1	2	3	4
Raw score	0–2	3	4	5	6

1 & 2 First and Second Names

Action: Re-present the three photographic portraits and ask for the names of the people portrayed as described in the test materials.

Response

	spontaneously	after prompt
Portrait 1		
First name recalled	☐	☐
Second name recalled	☐	☐
Portrait 2		
First name recalled	☐	☐
Second name recalled	☐	☐
Portrait 3		
First name recalled	☐	☐
Second name recalled	☐	☐

Scoring for First Names

Raw score

Calculate raw score as follows:

- Each first name recalled spontaneously = 2
- Each first name recalled after prompt = 1

☐ **Total raw score** (max = 6)

Profile score conversion table Profile score = ☐

Predicted (premorbid) intellectual band	Profile score 0	1	2	3	4
Below average	0	1	2–3	4	5–6
Average	0	1–2	3–4	5	6
Above average	0–1	2–3	4	5	6

Scoring for Second Names

Raw score

Calculate raw score as follows:

- Each second name recalled spontaneously = 2
- Each second name recalled after prompt = 1

☐ **Total raw score** (max = 6)

Profile score conversion table Profile score = ☐

Version	Predicted (premorbid) intellectual band	Profile score 0	1	2	3	4
1	Below average	0	1	2–3	4	5–6
	Average & above average	0–1	2	3–4	5	6
2	Below average	0	1	2–3	4–5	6
	Average & above average	0	1	2–4	5	6

3 Belongings

Action: Pause/prompt the subject for the hidden belongings as described in the test materials.

Response

	spontaneously	after prompt
Belonging 1 recalled	☐	☐
Belonging 2 recalled	☐	☐
Location 1 recalled	☐	☐
Location 2 recalled	☐	☐

Raw score

Calculate raw score as follows:

- Each belonging recalled spontaneously = 2
- Each belonging recalled after prompt = 1
- Each location recalled spontaneously = 2
- Each location recalled after prompt = 1

☐ **Total raw score** (max = 8)

Profile score conversion table Profile score = ☐

Note: Add 'Appointments' raw score (p.3) to 'Belongings' raw score (max = 12) to obtain one combined profile score

	Profile score 0	1	2	3	4
Combined raw score	0–8	9	10	11	12

Score summary

	Raw score	Profile score
1 First Names	☐	☐
2 Second Names	☐	☐
3 Belongings	☐ +	☐
4 Appointments	☐	
5 Picture Recognition	☐	☐
6 Story (immediate)	☐	☐
6 Story (delayed)	☐	☐
7 Face Recognition	☐	☐
8 Route (immediate)	☐	☐
8 Route (delayed)	☐	☐
9 Messages (immediate)	☐	☐
9 Messages (delayed)	☐	☐
10 & 11 Orientation and Date	☐	☐
Totals	☐	☐
	max = 157	max = 48

Appendix 7. Paced Audiory Serial Addition Test

POST

PASAT - Form B

Name T030 Date

PRACTICE	9+1	3	5	2	6	4	9	7	1	4
	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __

RATE #1	2+7	5	8	2	9	6	4	1	3	6
(3")	9 __	12__	13__	10__	11__	15__	10__	5 __	4 __	9 __
	3	6	2	8	4	9	1	6	7	2
	9 __	9 __	8 __	10__	12__	13__	10__	7 __	13__	9 __
	4	1	5	7	3	9	7	2	6	8
	6 __	5 __	6 __	12__	10__	12__	16__	9 __	8 __	14__
	4	2	5	8	5	9	3	7	1	4
	12__	6 __	7 __	13__	13__	14__	12__	10__	8 __	5 __
	2	4	3	6	1	7	3	8	3	9
	6 __	6 __	7 __	9 __	7 __	8 __	10__	11__	11__	12__
	1	3	5	2	6	4	9	7	1	4
	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __

Total Correct (raw) = _____ Percent Correct = _____

PRACTICE	3+8	2	7	9	1	8	5	2	6	4
	11__	10__	9 __	16__	10__	9 __	13__	7 __	8 __	10__

RATE #2	7+8	6	3	7	5	9	1	2	6	8
(2")	15__	14__	9 __	10__	12__	14__	10__	3 __	8 __	14__
	3	6	2	5	9	7	1	8	3	6
	11__	9 __	8 __	7 __	14__	16__	8 __	9 __	11__	9 __
	7	4	2	5	3	8	6	2	3	7
	13__	11__	6 __	7 __	8 __	11__	14__	8 __	5 __	10__
	3	5	2	8	5	3	7	4	1	5
	10__	8 __	7 __	10__	13__	8 __	10__	11__	5 __	6 __
	2	4	1	6	3	9	7	1	8	4
	7 __	6 __	5 __	7 __	9 __	12__	16__	8 __	9 __	12__
	6	2	5	8	1	9	7	2	8	3
	10__	8 __	7 __	13__	9 __	10__	16 __	9 __	10__	11__

Total Correct (raw) = _____ Percent Correct = _____

Appendix 8. Mayo-Portland Adaptability Inventory

Mayo-Portland Adaptability Inventory-4

Muriel D. Lezak, PhD, ABPP & James F. Malec, PhD, ABPP

Name: _____ Clinic # _____ Date _____

Person reporting (circle one): Single Professional Professional Consensus Person with brain injury Significant other: _____

Below each item, circle the number that best describes the level at which the person being evaluated experiences problems. Mark the greatest level of problem that is appropriate. Problems that interfere rarely with daily or valued activities, that is, less than 5% of the time, should be considered not to interfere. Write comments about specific items at the end of the rating scale.

For Items 1-20, please use the rating scale below.

0 None	1 Mild problem but does not interfere with activities; may use assistive device or medication	2 Mild problem; interferes with activities 5-24% of the time	3 Moderate problem; interferes with activities 25-75% of the time	4 Severe problem; interferes with activities more than 75% of the time

Part A. Abilities

1. **Mobility**: Problems walking or moving; balance problems that interfere with moving about
   0 1 2 3 4
2. **Use of hands**: Impaired strength or coordination in one or both hands
   0 1 2 3 4
3. **Vision**: Problems seeing; double vision; eye, brain, or nerve injuries that interfere with seeing
   0 1 2 3 4
4. ***Audition:** Problems hearing; ringing in the ears
   0 1 2 3 4
5. **Dizziness:** Feeling unsteady, dizzy, light-headed
   0 1 2 3 4
6. **Motor speech:** Abnormal clearness or rate of speech; stuttering
   0 1 2 3 4

7A. **Verbal communication**: Problems expressing or understanding language
   0 1 2 3 4

7B. **Nonverbal communication**: Restricted or unusual gestures or facial expressions; talking too much or not enough; missing nonverbal cues from others
   0 1 2 3 4

8. **Attention/Concentration:** Problems ignoring distractions, shifting attention, keeping more than one thing in mind at a time
   0 1 2 3 4
9. **Memory:** Problems learning and recalling new information
   0 1 2 3 4
10. **Fund of Information**: Problems remembering information learned in school or on the job; difficulty remembering information about self and family from years ago
    0 1 2 3 4
11. **Novel problem-solving:** Problems thinking up solutions or picking the best solution to new problems
    0 1 2 3 4
12. **Visuospatial abilities:** Problems drawing, assembling things, route-finding, being visually aware on both the left and right sides
    0 1 2 3 4

Part B. Adiustment

13. **Anxiety:** Tense, nervous, fearful, phobias, nightmares, flashbacks of stressful events
    0 1 2 3 4
14. **Depression:** Sad, blue, hopeless, poor appetite, poor sleep, worry, self-criticism
    0 1 2 3 4
15. **Irritability, anger, aggression:** Verbal or physical expressions of anger
    0 1 2 3 4
16. ***Pain and headache:** Verbal and nonverbal expressions of pain; activities limited by pain
    0 1 2 3 4
17. **Fatigue:** Feeling tired; lack of energy; tiring easily
    0 1 2 3 4
18. **Sensitivity to mild symptoms:** Focusing on thinking, physical or emotional problems attributed to brain injury; rate only how concern or worry about these symptoms affects current functioning over and above the effects of the symptoms themselves
    0 1 2 3 4
19. **Inappropriate social interaction:** Acting childish, silly, rude, behavior not fitting for time and place
    0 1 2 3 4
20. **Impaired self-awareness:** Lack of recognition of personal limitations and disabilities and how they interfere with everyday activities and work or school
    0 1 2 3 4

Use scale at the bottom of the page to rate item #21

21. **Family/significant relationships:** Interactions with close others; describe stress within the family or those closest to the person with brain injury; "family functioning" means cooperating to accomplish those tasks that need to be done to keep the household running

0 Normal stress within family or other close network of relationships	1 Mild stress that does not interfere with family functioning	2 Mild stress that interferes with family functioning 5-24% of the time	3 Moderate stress that interferes with family functioning 25-75% of the time	4 Severe stress that interferes with family functioning more than 75% of the time

MPAI-4 3/31/03

Part D: Pre-existing and associated conditions. The items below do not contribute to the total score but are used to identify special needs and circumstances. For each rate, pre-injury and post-injury status.

30. Alcohol use: Use of alcoholic beverages.

Pre-injury _____ Post-injury _____

0	No or socially acceptable use	**1**	Occasionally exceeds socially acceptable use but does not interfere with everyday functioning; current problem under treatment or in remission	**2**	Frequent excessive use that occasionally interferes with everyday functioning; possible dependence	**3**	Use or dependence interferes with everyday functioning; additional treatment recommended	**4**	Inpatient or residential treatment required

31. Drug use: Use of illegal drugs or abuse of prescription drugs.

Pre-injury _____ Post-injury _____

0	No or occasional use	**1**	Occasional use does not interfere with everyday functioning; current problem under treatment or in remission	**2**	Frequent use that occasionally interferes with everyday functioning; possible dependence	**3**	Use or dependence interferes with everyday functioning; additional treatment recommended	**4**	Inpatient or residential treatment required

32. Psychotic Symptoms: Hallucinations, delusions, other persistent severely distorted perceptions of reality.

Pre-injury _____ Post-injury _____

0	None	**1**	Current problem under treatment or in remission; symptoms do not interfere with everyday functioning	**2**	Symptoms occasionally interfere with everyday functioning but no additional evaluation or treatment recommended	**3**	Symptoms interfere with everyday functioning; additional treatment recommended	**4**	Inpatient or residential treatment required

33. Law violations: History before and after injury.

Pre-injury _____ Post-injury _____

0	None or minor traffic violations only	**1**	Conviction on one or two misdemeanors other than minor traffic violations	**2**	History of more than two misdeameanors other than minor traffic violations	**3**	Single felony conviction	**4**	Repeat felony convictions

34. Other condition causing physical impairment: Physical disability due to medical conditions other than brain injury, such as, spinal cord injury, amputation. Use scale below #35.

Pre-injury _____ Post-injury _____

35. Other condition causing cognitive impairment: Cognitive disability due to nonpsychiatric medical conditions other than brain injury, such as, dementia, stroke, developmental disability.

Pre-injury _____ Post-injury _____

0	None	**1**	Mild problem but does not interfere with activities; may use assistive device or medication	**2**	Mild problem; interferes with activities 5-24% of the time	**3**	Moderate problem; interferes with activities 25-75% of the time	**4**	Severe problem; interferes with activities more than 75% of the time

Comments:

Item #

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Scoring Worksheet

Items with an asterisk (4, 16, 27, 28/28A) require rescoring as specified below before Raw Scores are summed and referred to Reference Tables to obtain Standard Scores. Because items 22-24 contribute to both the Adjustment Subscale and the Participation Subscale, the Total Score will be less than the sum of the three subscales.

Abilities Subscale

Rescore item 4. Original score = _____
If original score = 0, new score = 0
If original score = 1, 2, or 3, new score = 1
If original score = 4, new score = 3

A. New score for item 4 = _____
B. Sum of scores for items 1-3 and 5-12 = _____
(use highest score for 7A or 7B)

Sum of A and B = Raw Score for Abilities subscale = _____ (place in Table below)

Adjustment Subscale

Rescore item 16. Original score = _____
If original score = 0, new score = 0
If original score = 1 or 2, new score = 1.
If original score = 3 or 4, new score = 2

C. New score for item 16 = _____
D. Sum of scores for items 13-15 and 17-24 _____

Sum of C and D = Raw Score for Adjustment Subscale _____ (place in Table below)

Participation Subscale

Rescore item 27. Original score = _____
If original score = 0 or 1, new score = 0
If original score = 2 or 3, new score = 1
If original score = 4, new score = 3

Rescore item 28A or 28B. Original score = _____
If original score = 0, new score = 0
If original score = 1 or 2, new score = 1
If original score = 3 or 4, new score = 3

E. New score for item 27 = _____
F. New score for item 28Aor 28B = _____
G. Sum of scores for items 22-24 = _____ (place in Table below)
H. Sum of scores for items 25, 26, 29 = _____

Sum of E through H = Raw Score for Participation Subscale = _____ (place in Table below)

Use Reference Tables to Convert Raw Scores to Standard Scores

	Raw Scores (from worksheet above)	**Standard** (Obtain from appropriate reference Table)
I. Ability Subscale (Items 1-12)	_____	_____
II. Adjustment Subscale (Items 13-24)	_____	_____
III. Participation Subscale (Items 22-29)	_____	_____
IV. Subtotal of Subscale Raw Scores (I-III)	_____	
V. Sum of scores for items 22-24	_____	
VI. Subtract from V. from IV = Total Score	_____	_____

MPAI-4 3/31/03

Appendix 9. Aerobic Capacity Descriptive Statistics

Basic Statistical Measures			
Location		**Variability**	
Mean	4.200000	**Std Deviation**	1.98830
Median	3.600000	**Variance**	3.95333
Mode	.	**Range**	4.50000
		Interquartile Range	4.10000

Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.84227	**Pr < W**	0.1043
Kolmogorov-Smirnov	**D**	0.232296	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.079605	**Pr > W-Sq**	0.1836
Anderson-Darling	**A-Sq**	0.499236	**Pr > A-Sq**	0.1395

Appendix 10. RBMT-E Descriptive Statistics

Test	N Obs	Variable	N	Mean	Std Dev	Minimum	Maximum
Pre	7	Prof_A	7	1.57	0.53	1.00	2.00
		Prof_B	7	1.14	1.46	0.00	4.00
		Prof_D	7	1.57	1.62	0.00	4.00
		Prof_E	7	1.29	0.95	0.00	2.00
		Prof_F	7	1.29	1.25	0.00	3.00
		Prof_G	7	1.86	0.69	1.00	3.00
		Prof_H	7	1.29	1.11	0.00	3.00
		Prof_I	7	2.43	1.62	0.00	4.00
		Prof_J	7	2.71	1.38	1.00	4.00
		Prof_K	7	3.71	0.49	3.00	4.00
		Prof_L	7	2.86	1.21	1.00	4.00
		Prof_M	7	2.00	1.41	0.00	4.00
		Prof_Total	7	23.71	5.22	17.00	31.00
Post	7	Prof_A	7	1.29	0.76	0.00	2.00
		Prof_B	7	1.14	0.90	0.00	2.00
		Prof_D	7	3.14	1.57	0.00	4.00
		Prof_E	7	1.86	0.90	0.00	3.00
		Prof_F	7	1.57	0.79	1.00	3.00
		Prof_G	7	1.43	0.79	1.00	3.00
		Prof_H	7	1.57	1.72	0.00	4.00
		Prof_I	7	4.00	0.00	4.00	4.00
		Prof_J	7	3.29	1.25	1.00	4.00
		Prof_K	7	4.00	0.00	4.00	4.00
		Prof_L	7	4.00	0.00	4.00	4.00
		Prof_M	7	2.43	1.51	0.00	4.00
		Prof_Total	7	29.71	5.96	20.00	38.00

Total RBMT-E Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.865021	**Pr < W**	0.1678
Kolmogorov-Smirnov	**D**	0.258437	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.071062	**Pr > W-Sq**	0.2374
Anderson-Darling	**A-Sq**	0.456575	**Pr > A-Sq**	0.1880

Appendix 11. PASAT Descriptive Statistics

Test	N Obs	Variable	N	Mean	Std Dev	Minimum	Maximum
Pre	7	rate_1	7	36.00	13.93	13.00	50.00
		rate_2	7	24.29	11.06	12.00	38.00
		rate_1_perc	7	0.60	0.23	0.22	0.83
		rate_2_perc	7	0.40	0.18	0.20	0.63
Post	7	rate_1	7	43.14	15.93	18.00	59.00
		rate_2	7	31.00	13.63	10.00	45.00
		rate_1_perc	7	0.72	0.27	0.30	0.98
		rate_2_perc	7	0.52	0.23	0.17	0.75

PASAT Slow Speed Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.925609	**Pr < W**	0.5142
Kolmogorov-Smirnov	**D**	0.203301	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.05015	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.302117	**Pr > A-Sq**	>0.2500

PASAT Fast Speed Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.922082	**Pr < W**	0.4857
Kolmogorov-Smirnov	**D**	0.24016	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.075657	**Pr > W-Sq**	0.2085
Anderson-Darling	**A-Sq**	0.406498	**Pr > A-Sq**	>0.2500

Appendix 12. WCST-64 Descriptive Statistics

Test	N Obs	Variable	N	Mean	Std Dev	Minimum	Maximum
Pre	7	Cat__Completed	7	2.29	1.38	0.00	4.00
		Con__Lev__Resp	7	36.86	16.67	9.00	55.00
		NonP_Errors	7	10.14	3.29	6.00	15.00
		Pers_Errors	7	10.00	7.07	2.00	23.00
		Pers_Resp	7	11.43	8.12	2.00	26.00
		Stand_Errors	7	91.14	16.10	63.00	109.00
		Stand_Pers_Error	7	95.14	17.77	67.00	123.00
		Stand_pers_resp	7	87.14	16.00	62.00	107.00
		T_Con__Lev__Resp	7	41.86	11.26	24.00	57.00
		T_NonP_Errors	7	41.57	6.00	33.00	50.00
		T_Pers_Errors	7	46.71	11.73	28.00	65.00
		T_Pers__Resp	7	47.71	8.77	36.00	62.00
		T_score_Errors	7	44.00	10.89	25.00	56.00
		Tot_Errors	7	20.14	10.25	9.00	38.00
		Tot_correct_raw	7	43.86	10.25	26.00	55.00
		stan_Con__Lev_Resp	7	87.71	16.89	61.00	110.00
Post	7	Cat__Completed	7	3.57	0.79	3.00	5.00
		Con__Lev__Resp	7	51.14	1.68	49.00	53.00
		NonP_Errors	7	6.86	2.12	3.00	9.00
		Pers_Errors	7	4.71	1.25	3.00	7.00
		Pers_Resp	7	4.71	1.25	3.00	7.00
		Stand_Errors	7	106.14	5.87	98.00	115.00
		Stand_Pers_Error	7	107.86	11.48	94.00	124.00
		Stand_pers_resp	7	108.29	9.66	94.00	121.00
		T_Con__Lev__Resp	7	53.29	5.79	46.00	62.00
		T_NonP_Errors	7	47.86	6.12	42.00	59.00
		T_Pers_Errors	7	55.29	7.85	46.00	66.00
		T_Pers__Resp	7	55.43	6.43	46.00	64.00
		T_score_Errors	7	54.14	3.89	49.00	60.00
		Tot_Errors	7	11.57	1.51	10.00	14.00
		Tot_correct_raw	7	52.43	1.51	50.00	54.00
		stan_Con__Lev_Resp	7	105.00	8.76	94.00	118.00

Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.967066	**Pr < W**	0.8766
Kolmogorov-Smirnov	**D**	0.185145	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.036615	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.223839	**Pr > A-Sq**	>0.2500

Appendix 13. MPAI-4 Descriptive Statistics

Test	N Obs	Variable	N	Mean	Std Dev	Minimum	Maximum
Pre	7	Abilities_raw	7	14.43	4.35	6.00	19.00
		Adjust_raw	7	22.29	10.69	8.00	39.00
		part_raw	7	13.14	6.64	0.00	20.00
		StandAbil	7	48.57	4.61	39.00	53.00
		StandAdj	7	54.00	8.70	42.00	68.00
		StandPart	7	48.00	19.88	4.00	61.00
		StandTotal	7	53.71	8.32	39.00	66.00
Post	7	Abilities_raw	7	8.00	3.74	3.00	12.00
		Adjust_raw	7	10.14	8.36	2.00	26.00
		part_raw	7	8.00	5.29	0.00	13.00
		StandAbil	7	40.00	8.35	25.00	47.00
		StandAdj	7	40.29	12.63	19.00	57.00
		StandPart	7	40.29	16.39	7.00	52.00
		StandTotal	7	40.43	14.26	11.00	51.00

MPAI-4 Standardized Total Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.923362	**Pr < W**	0.4960
Kolmogorov-Smirnov	**D**	0.179327	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.046413	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.292219	**Pr > A-Sq**	>0.2500

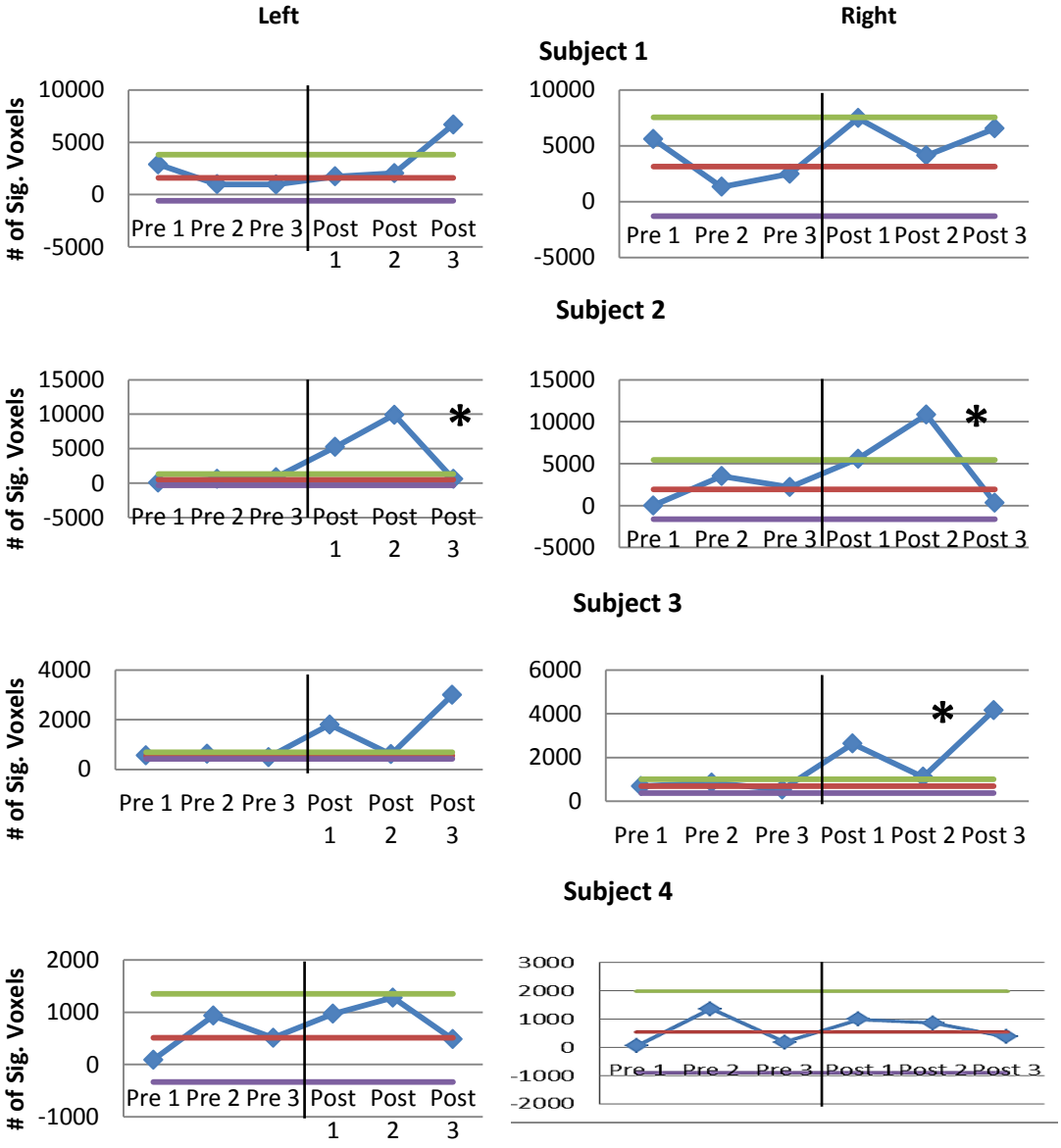
Appendix 14. MPAI-4 Sub-test Descriptive Statistics

MPAI-4 Standardized Abilities Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.962109	**Pr < W**	0.8366
Kolmogorov-Smirnov	**D**	0.140875	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.023812	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.174299	**Pr > A-Sq**	>0.2500

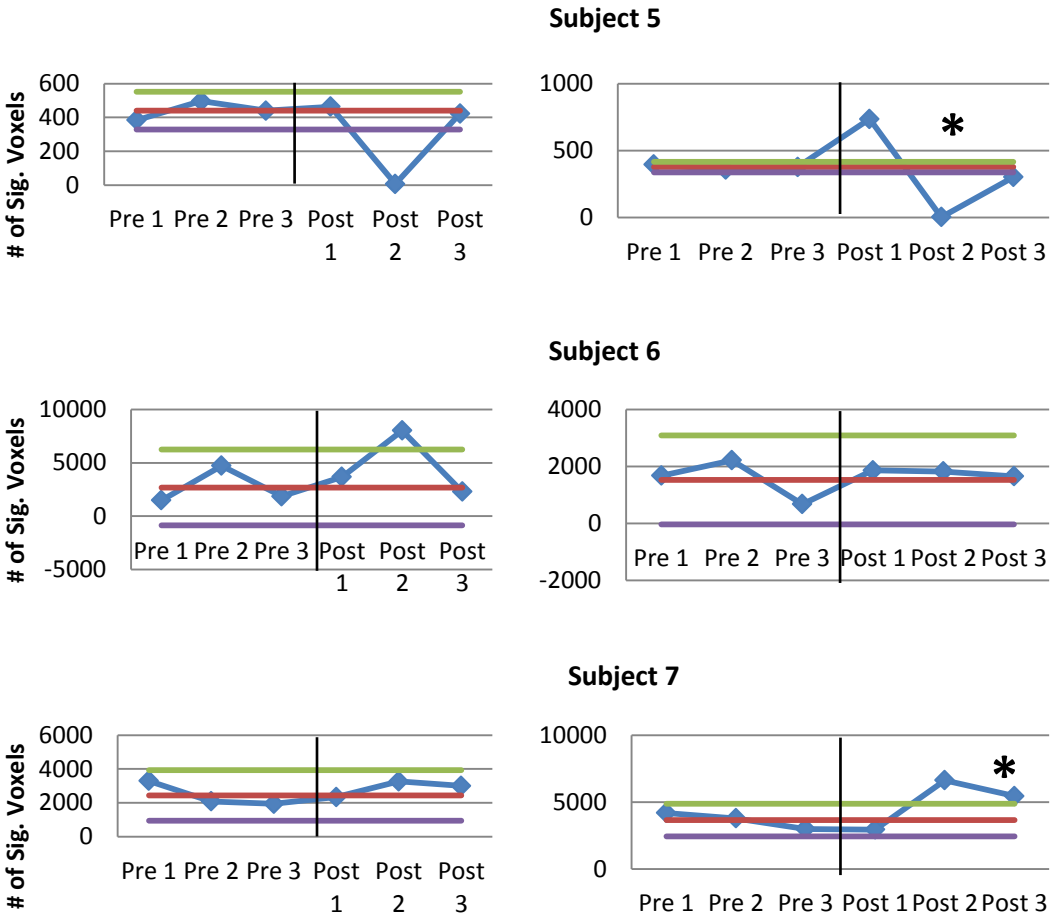
MPAI-4 Standardized Adjustment Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.891578	**Pr < W**	0.2830
Kolmogorov-Smirnov	**D**	0.202807	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.063438	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.38206	**Pr > A-Sq**	>0.2500

MPAI -4 Standardized Participation Tests for Normality				
Test	**Statistic**		**p Value**	
Shapiro-Wilk	**W**	0.899693	**Pr < W**	0.3291
Kolmogorov-Smirnov	**D**	0.200493	**Pr > D**	>0.1500
Cramer-von Mises	**W-Sq**	0.046719	**Pr > W-Sq**	>0.2500
Anderson-Darling	**A-Sq**	0.337907	**Pr > A-Sq**	>0.2500

Appendix 15: 0 Back DLPFC Voxel Count

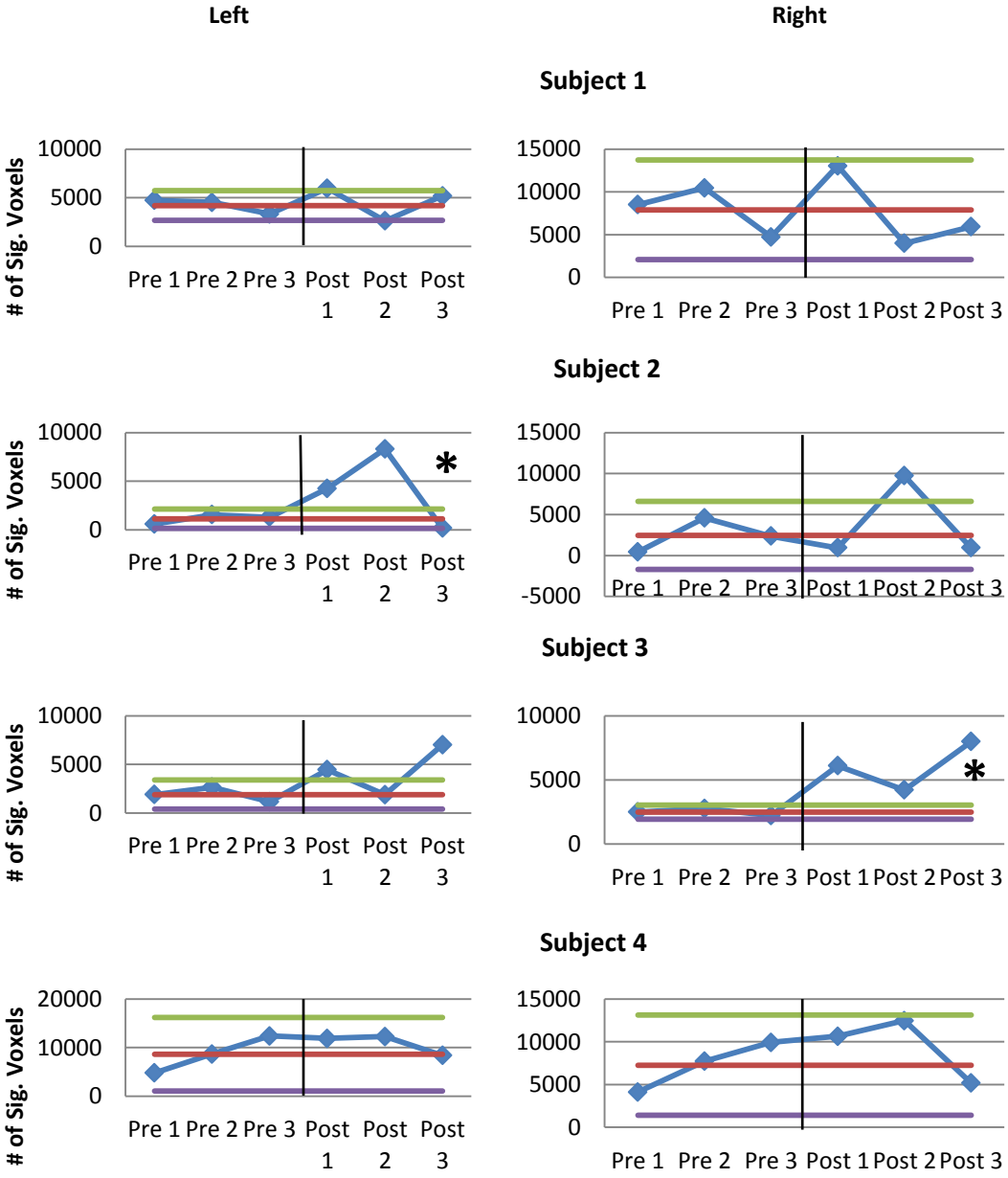


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

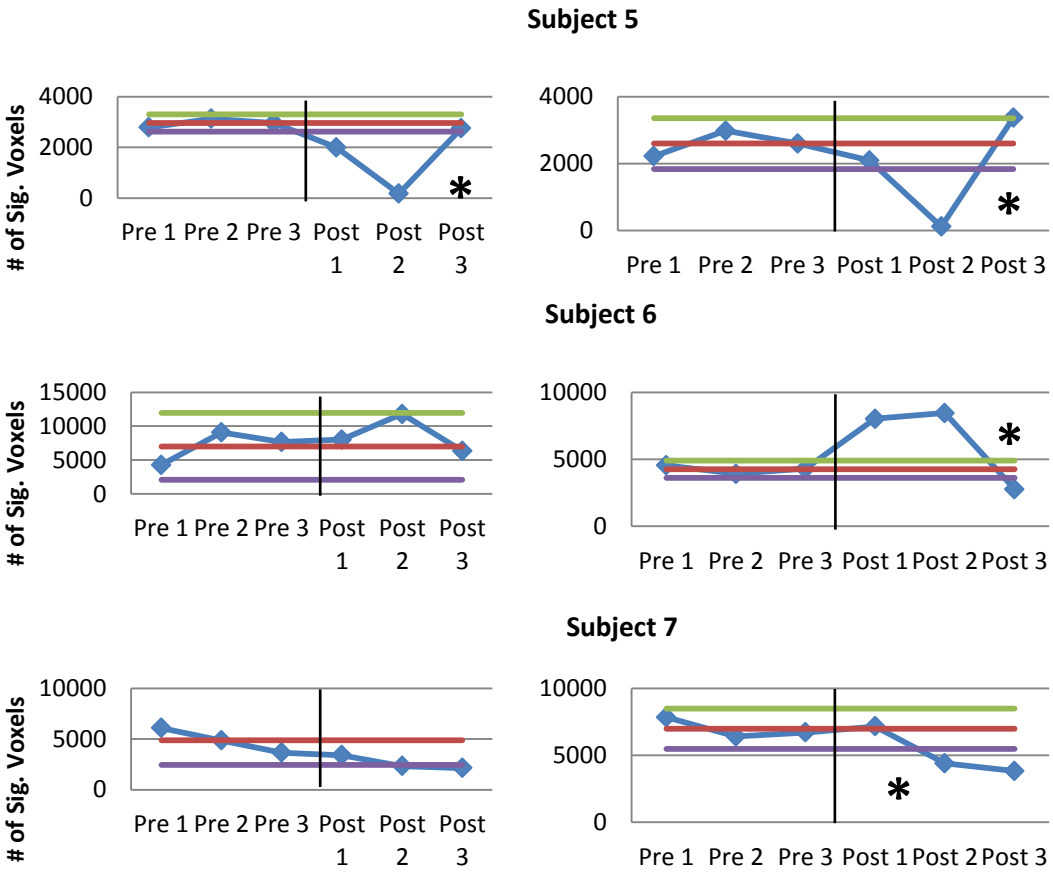


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 15: 2-Back DLPFC Voxel Count

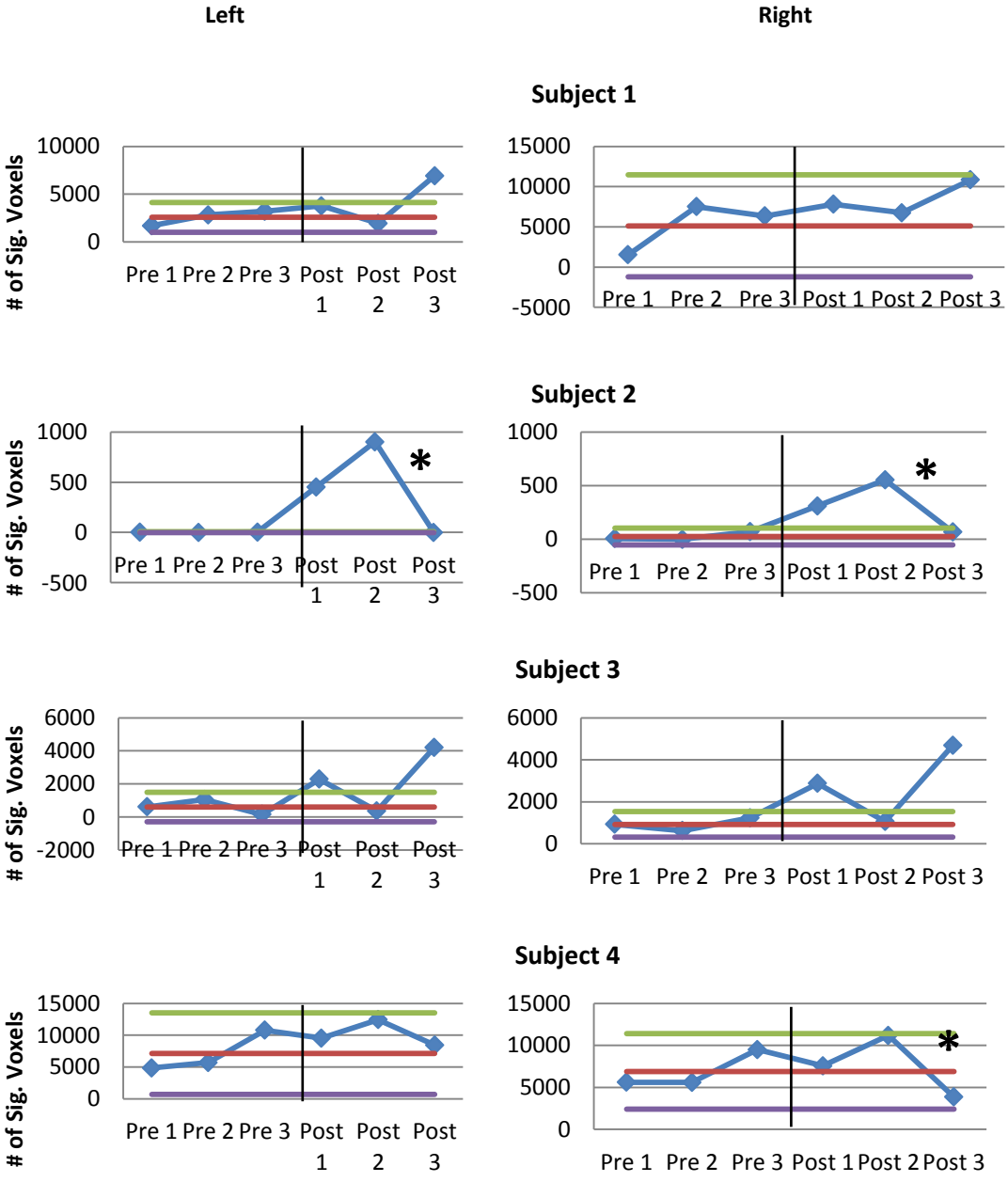


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

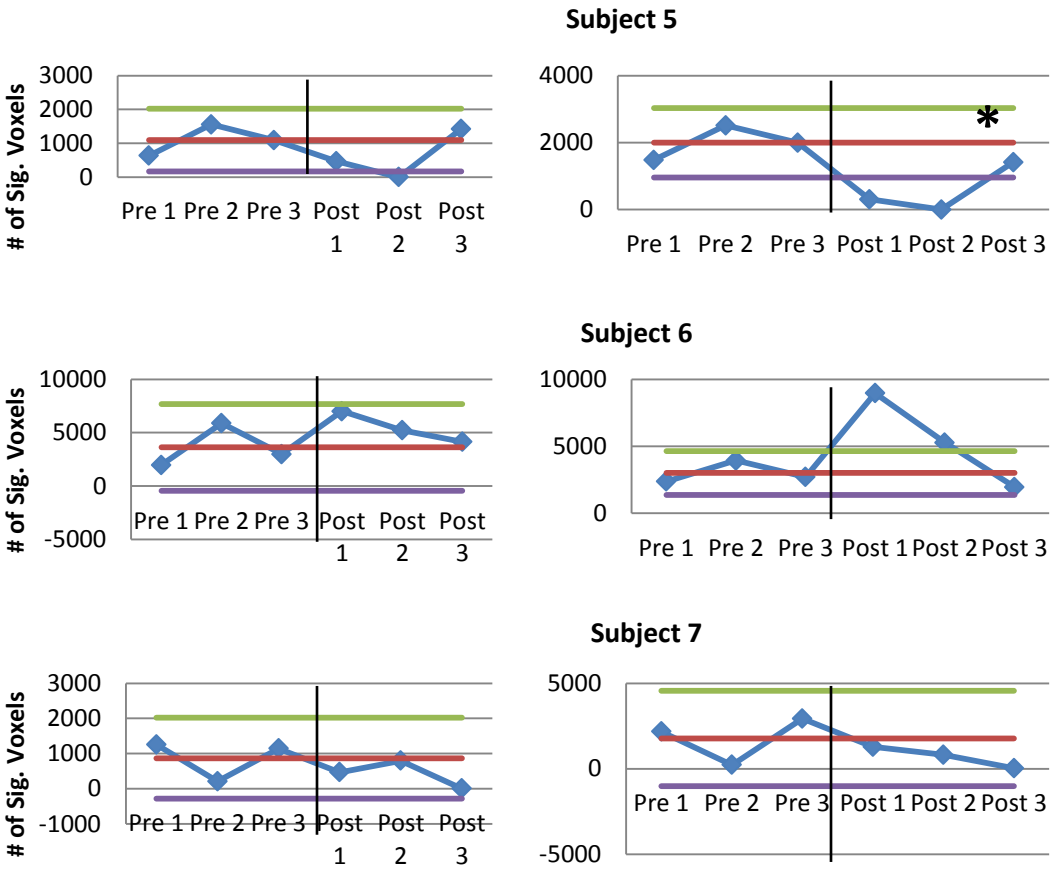


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 15: -0+2-Back DLPFC Voxel Count

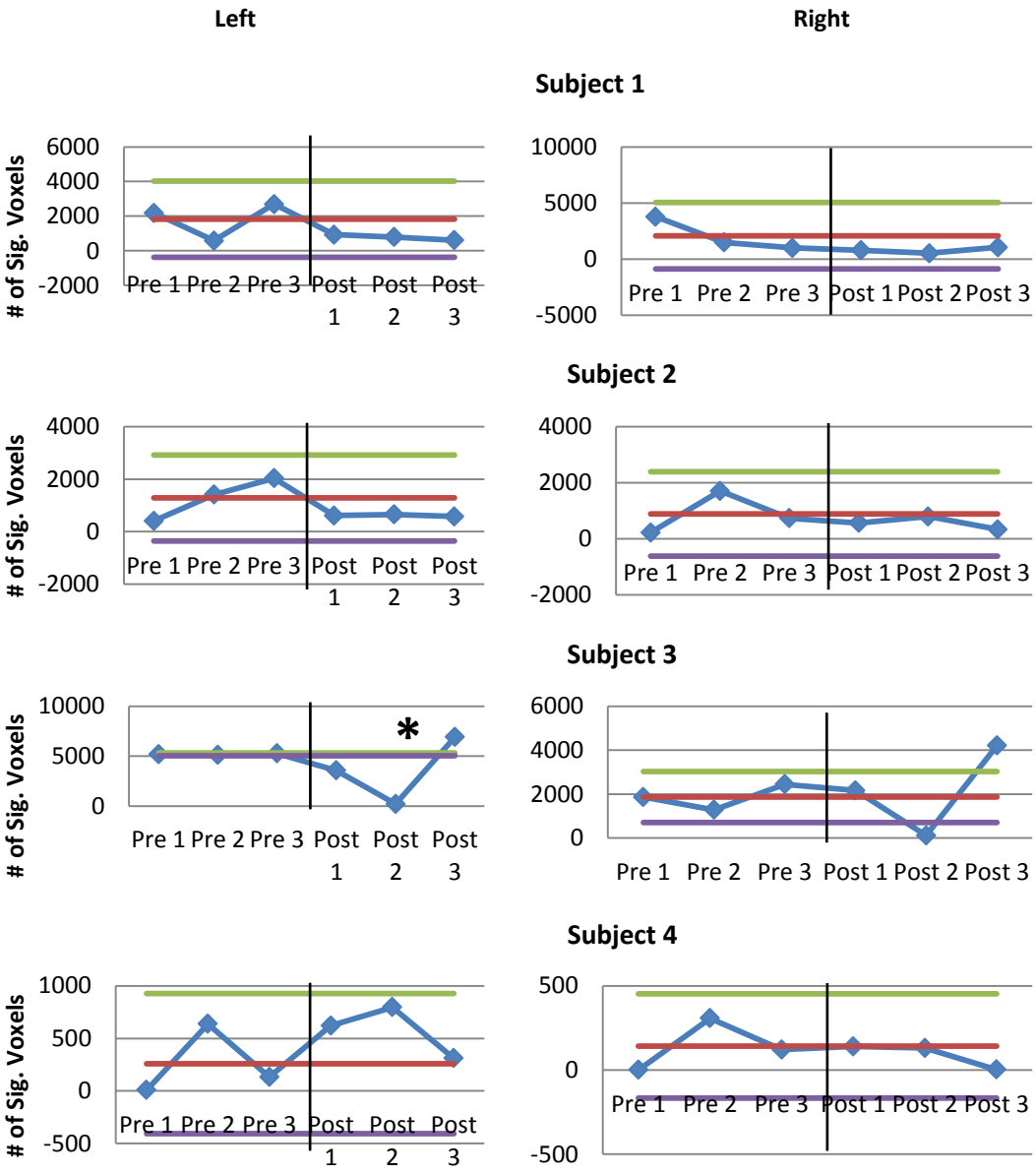


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

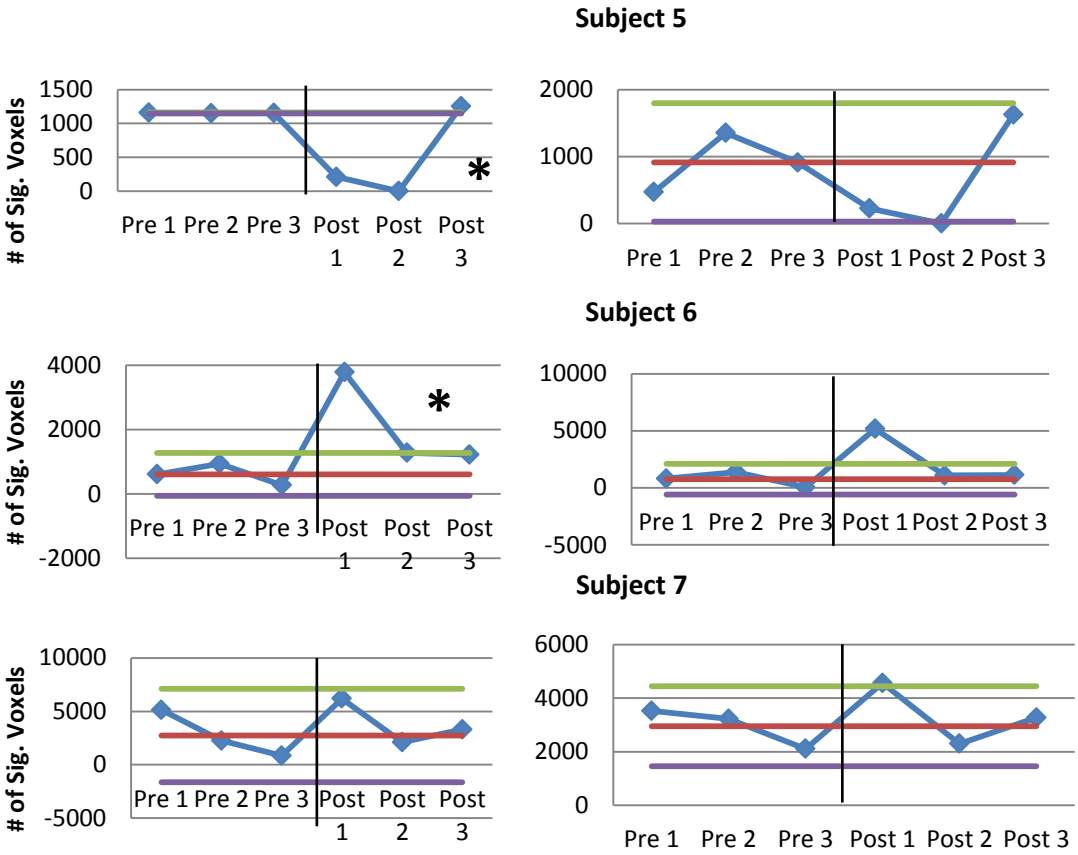


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 16: 0-Back Precuneus Voxel Count

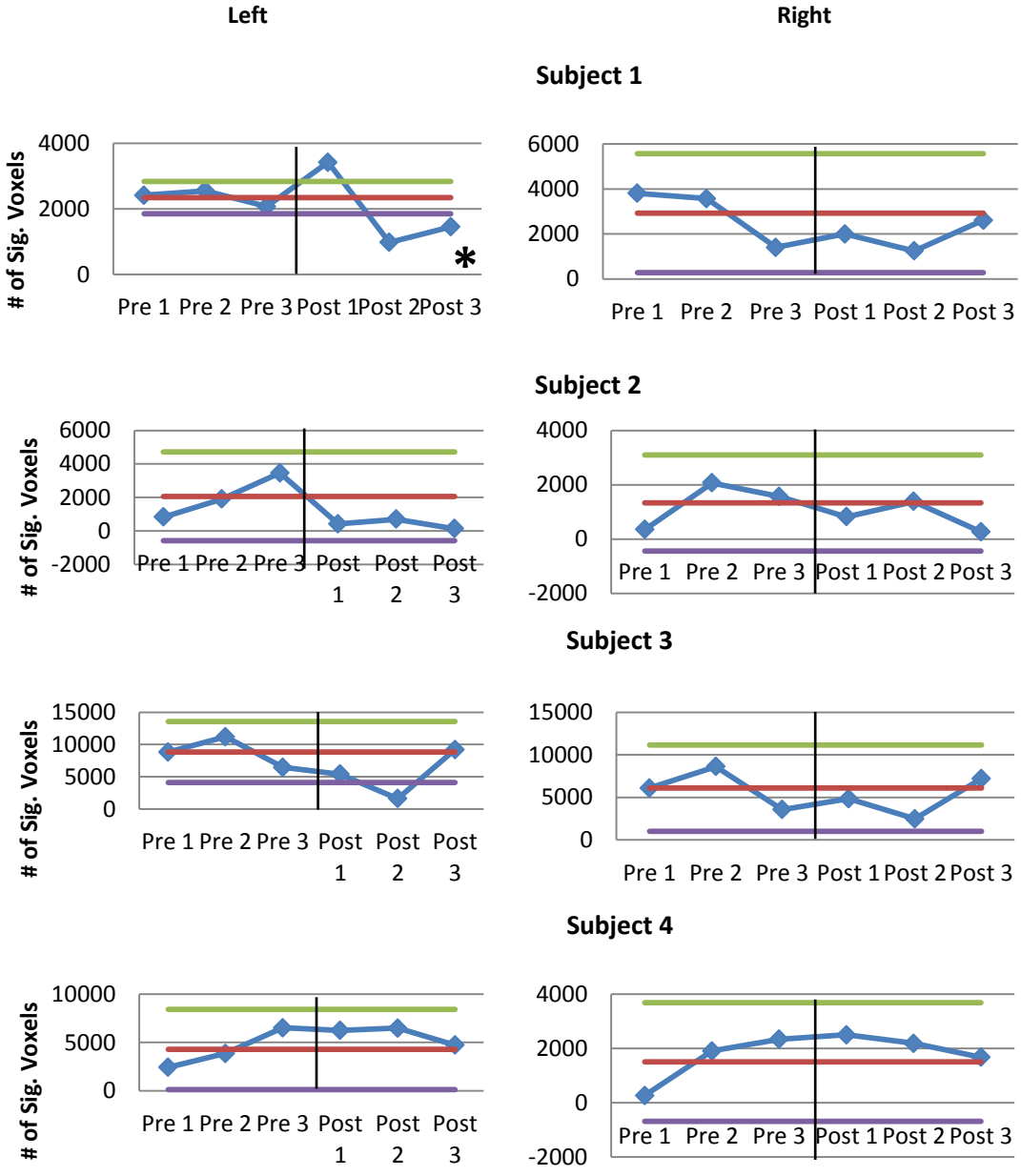


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

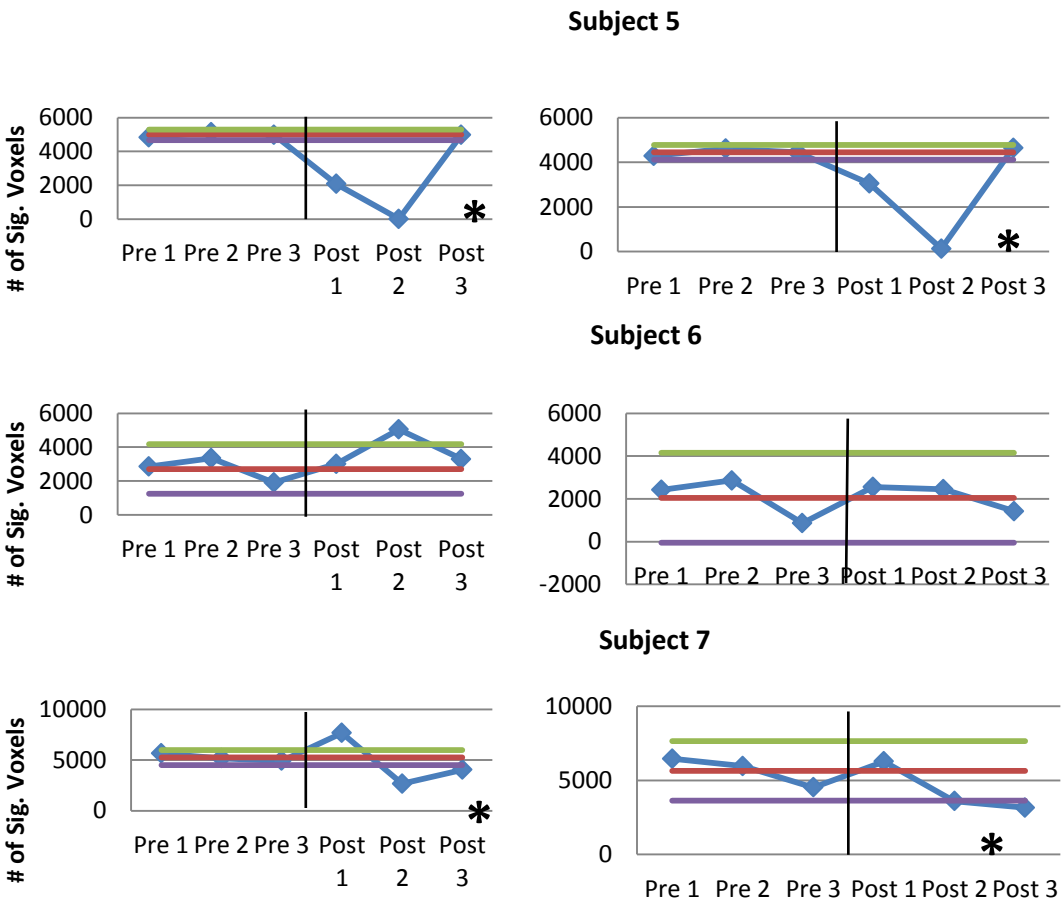


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 16: 2-Back Precuneus Voxel Count

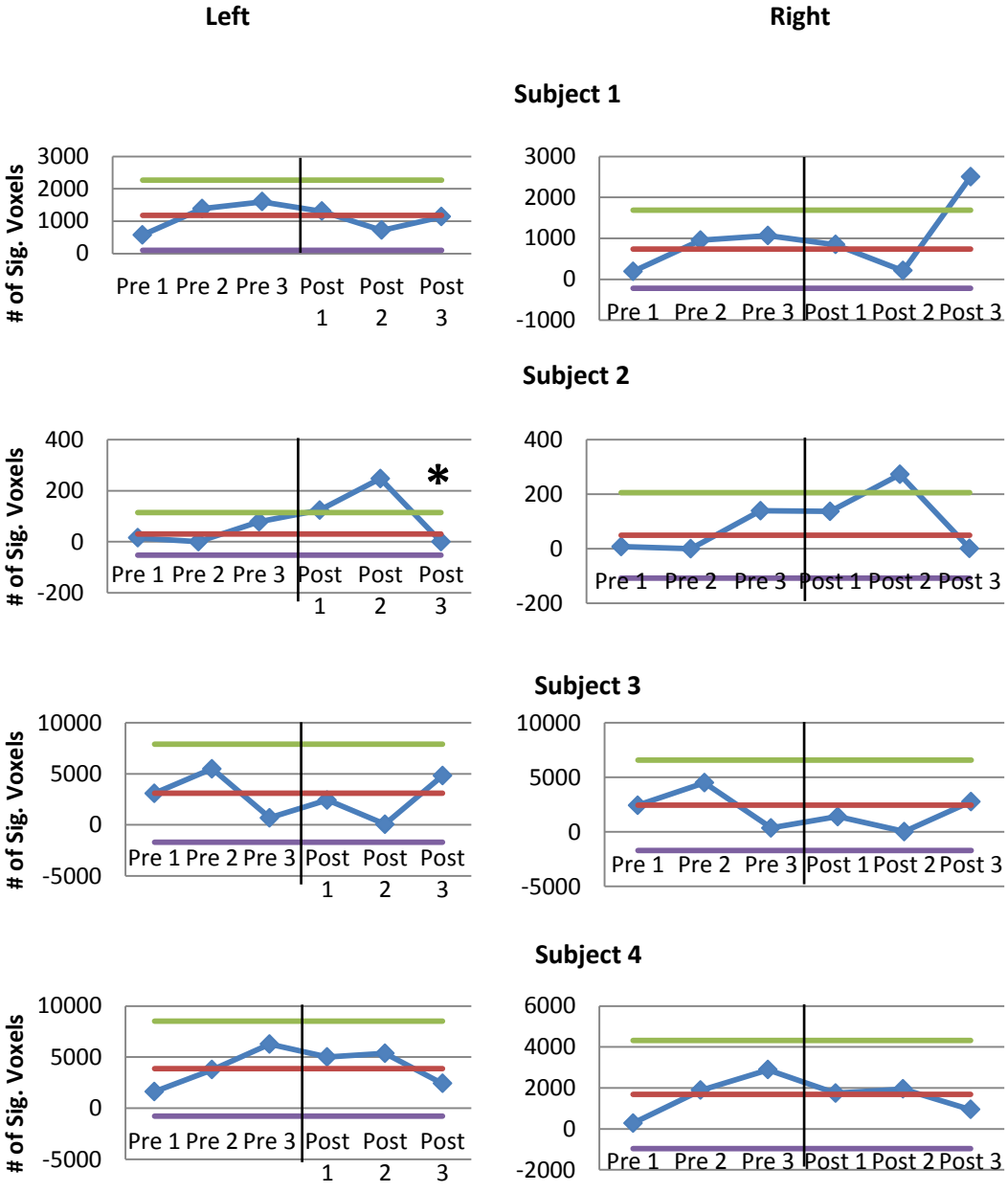


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

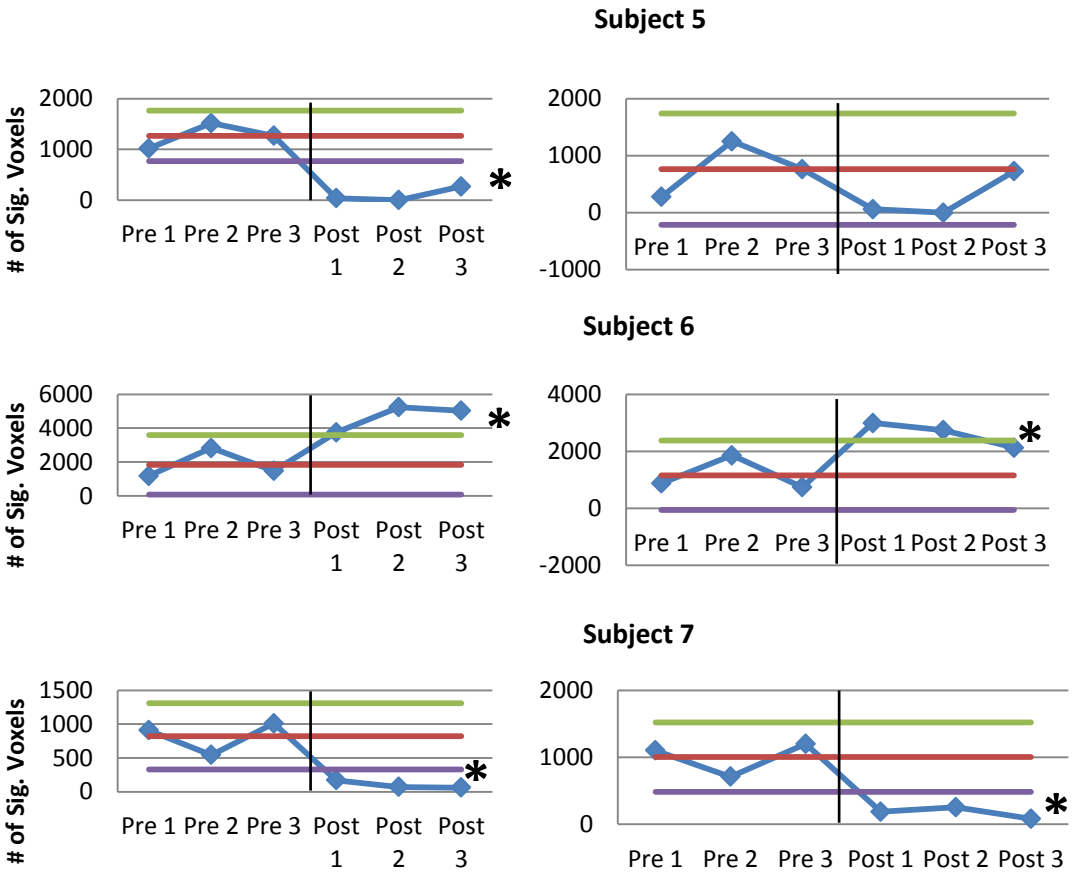


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 16: -0+2-Back Precuneus Voxel Count

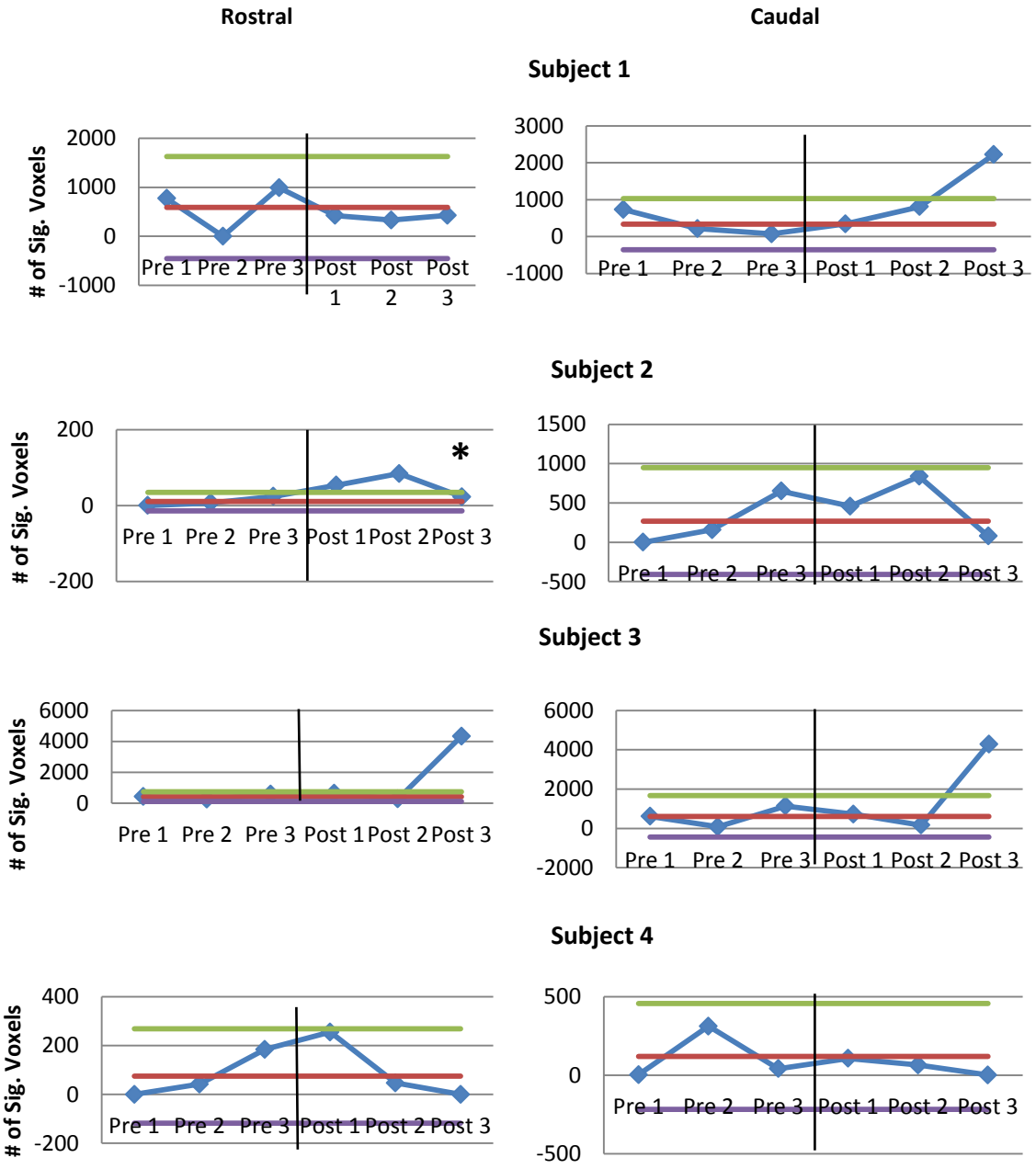


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention



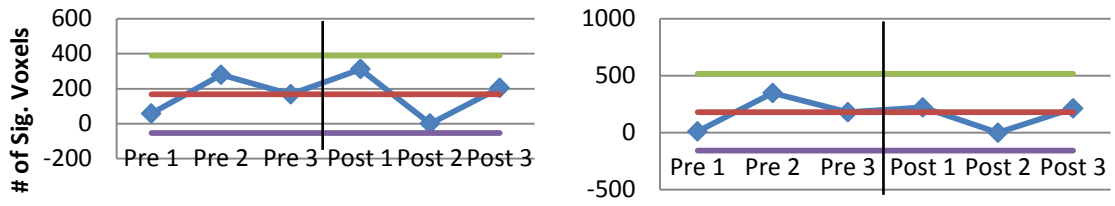
Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 17: 0-Back ACC Voxel Count

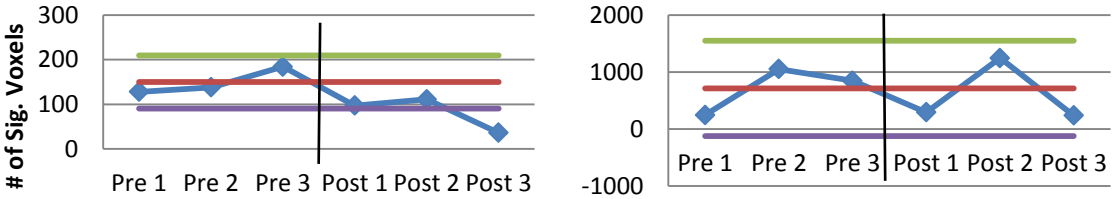


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

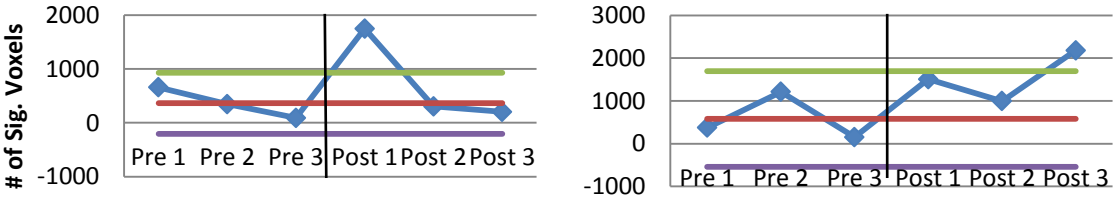
Subject 5



Subject 6



Subject 7

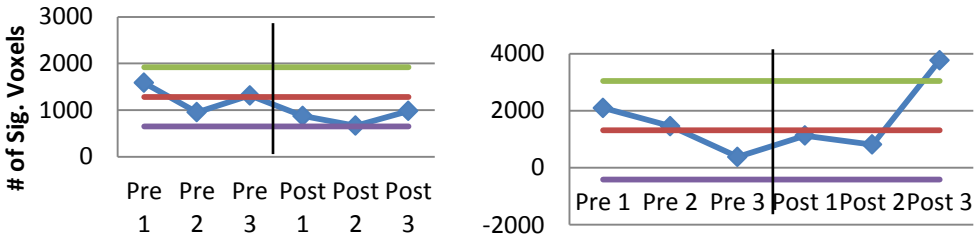


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

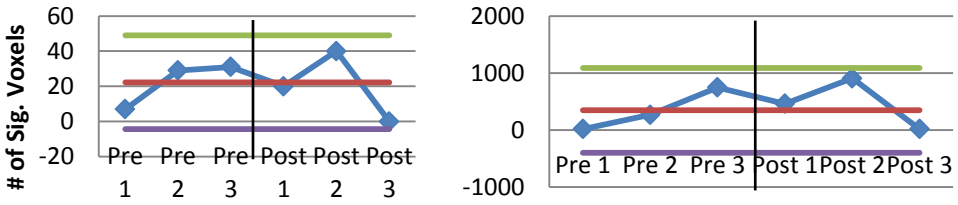
Appendix 17: 2-Back ACC Voxel Count

Rostral **Caudal**

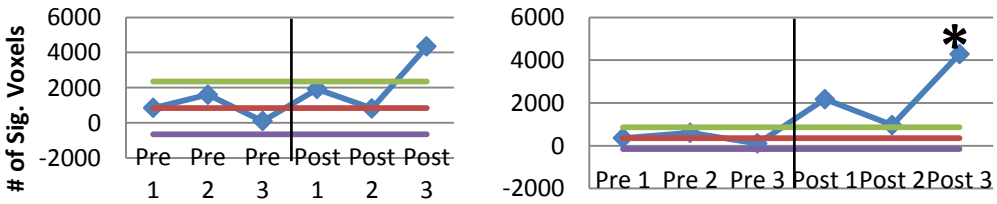
Subject 1



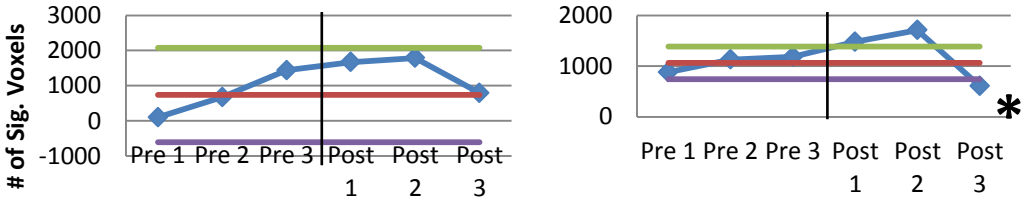
Subject 2



Subject 3

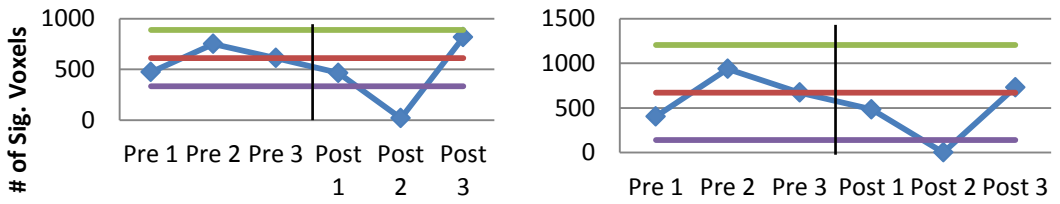


Subject 4

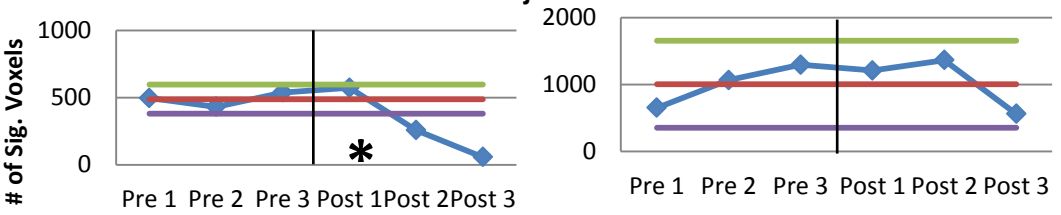


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

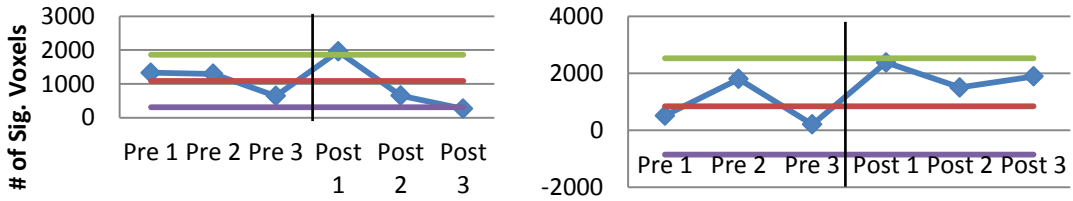
Subject 5



Subject 6

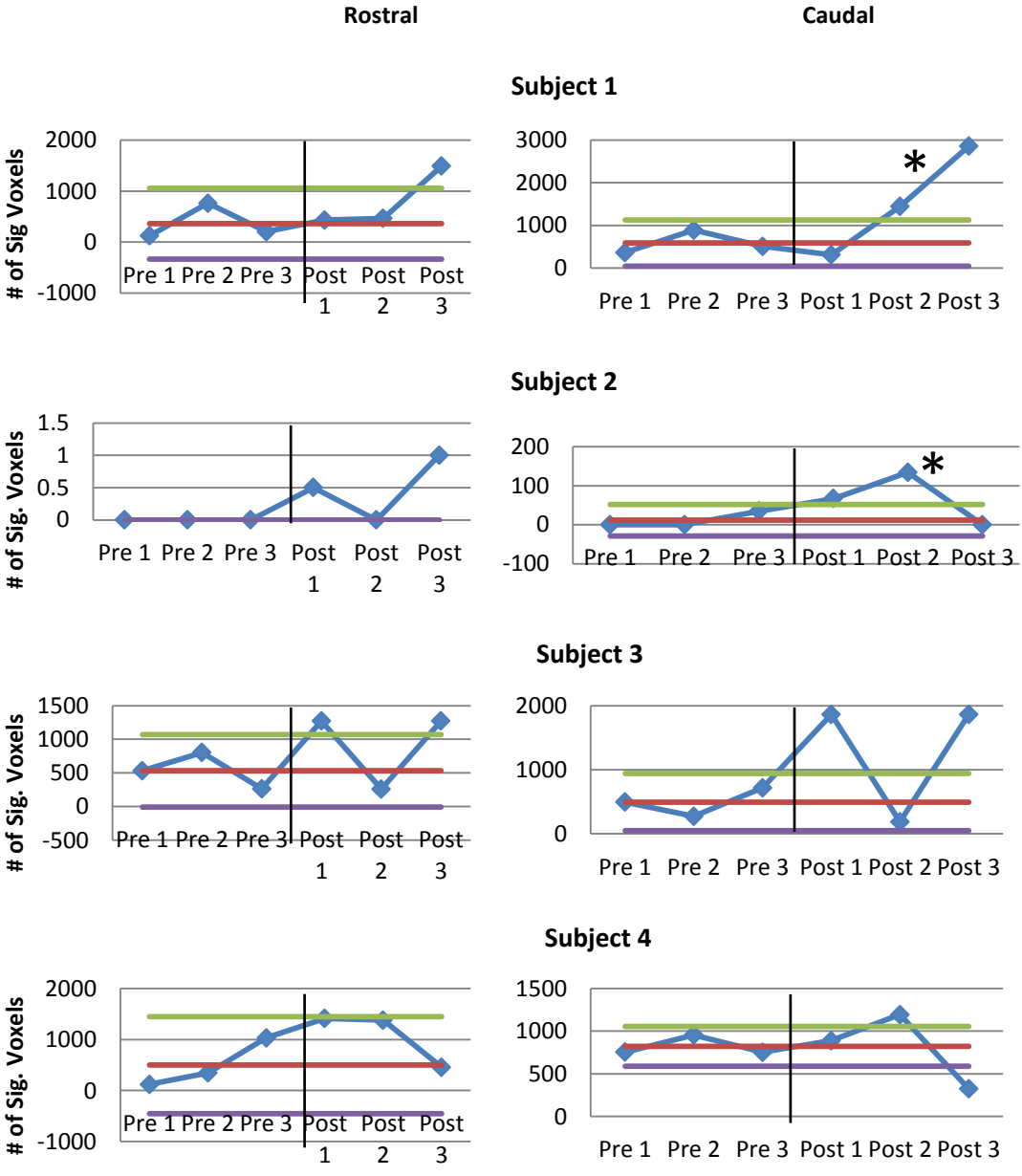


Subject 7

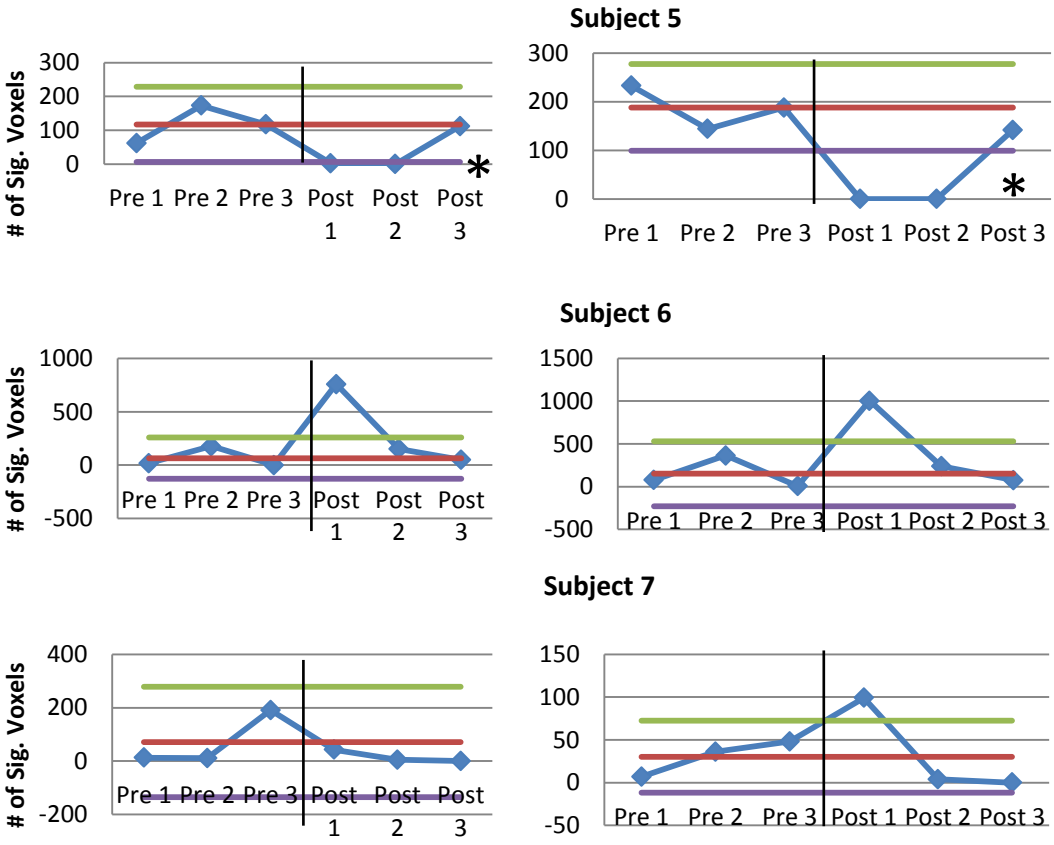


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 17: -0+2 Back ACC Voxel Count

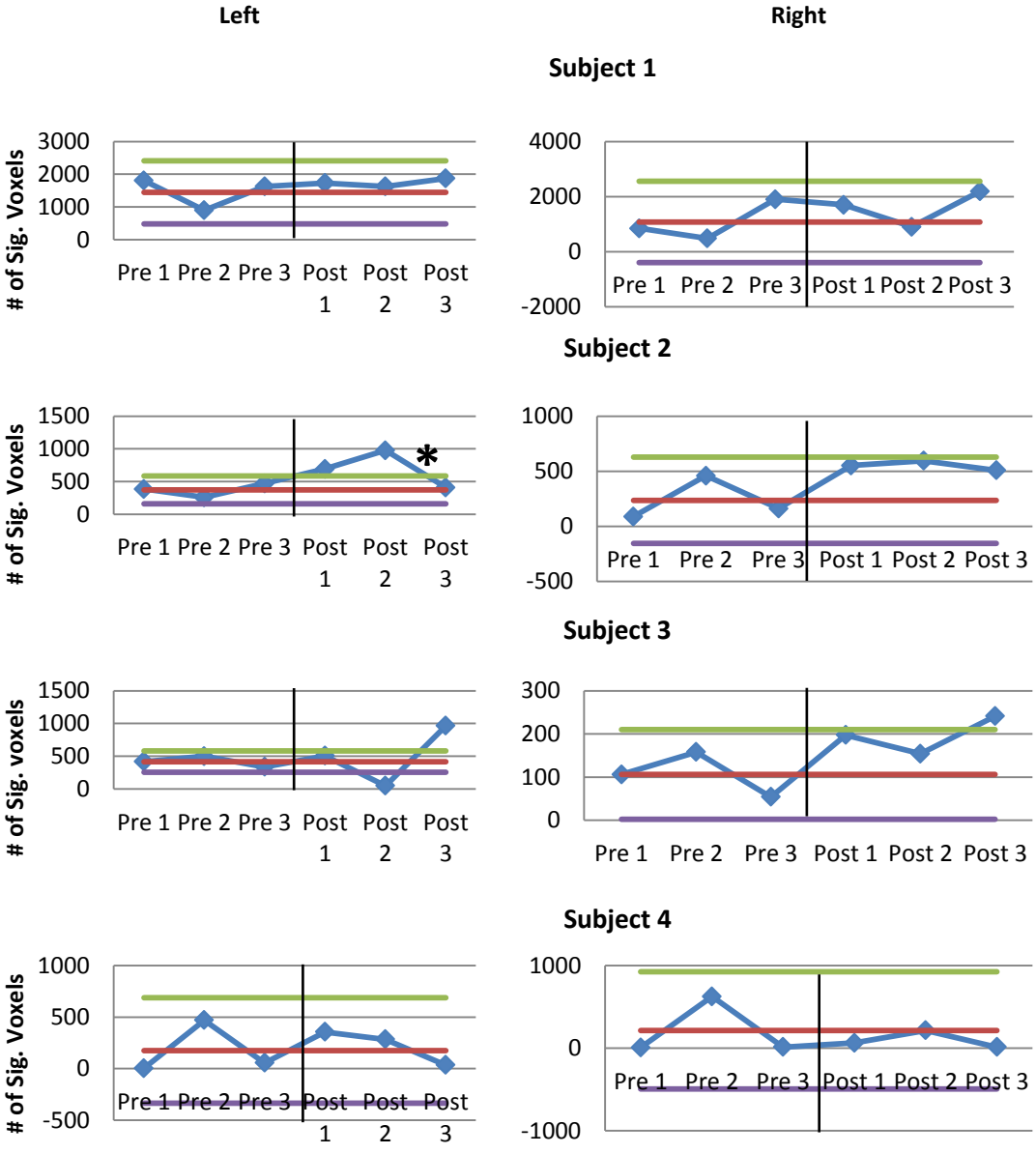


Upper bold line indicates 2 SD above mean; Center bold line indicates SD
Lower bold line indicates 2SD below mean; Vertical bold line indicates aerobic intervention

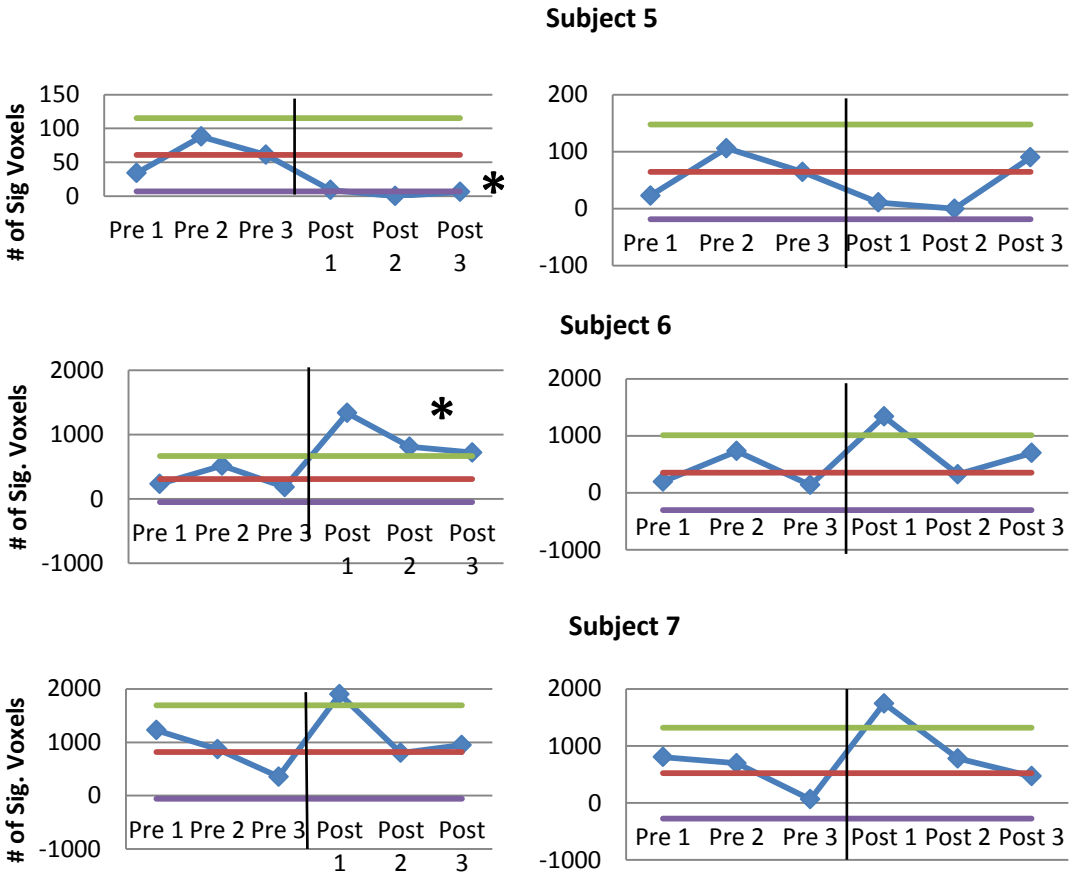


Upper bold line indicates 2 SD above mean; Center bold line indicates SD
Lower bold line indicates 2SD below mean; Vertical bold line indicates aerobic intervention

Appendix 18: 0 Back PCC Voxel Count

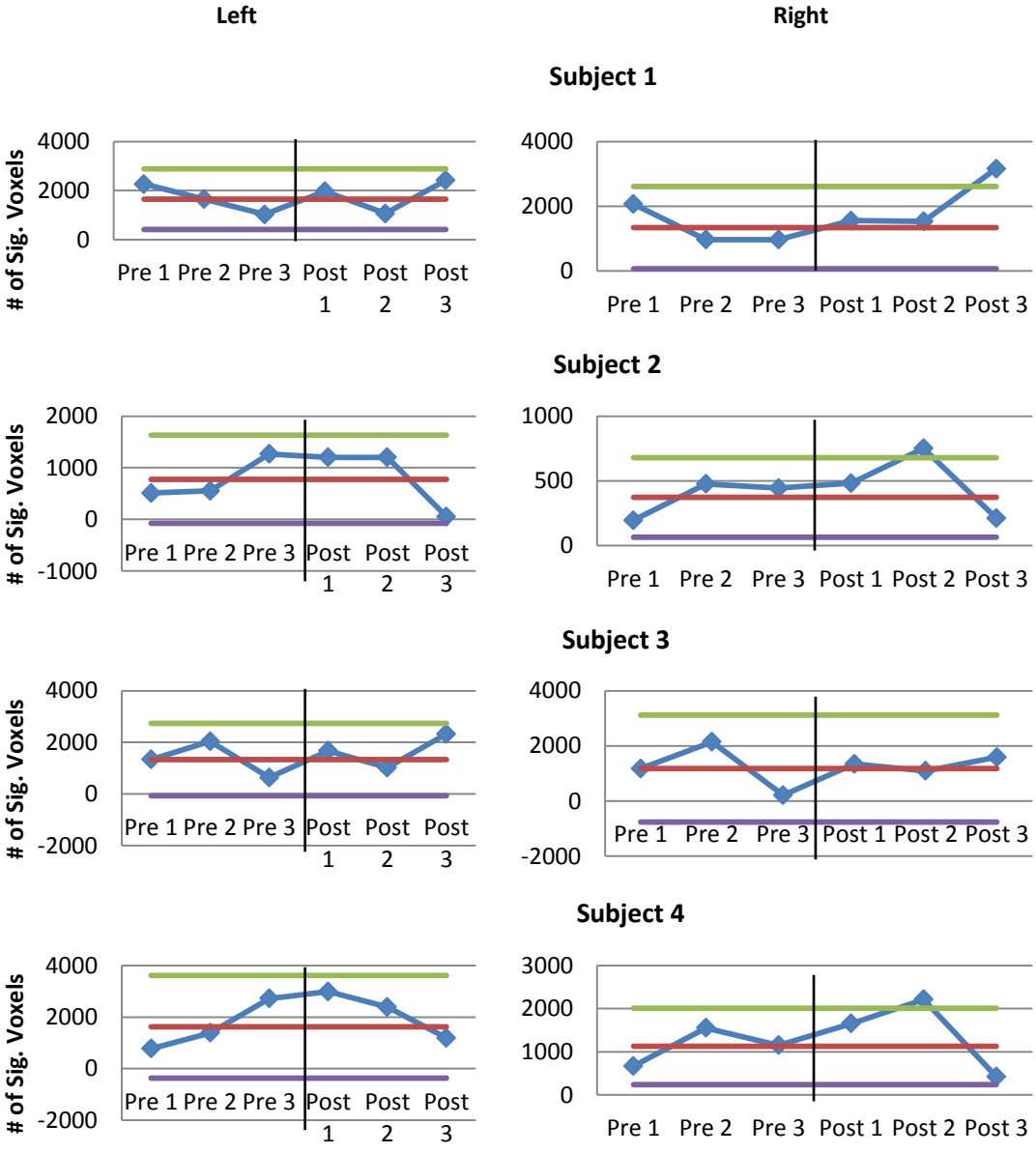


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

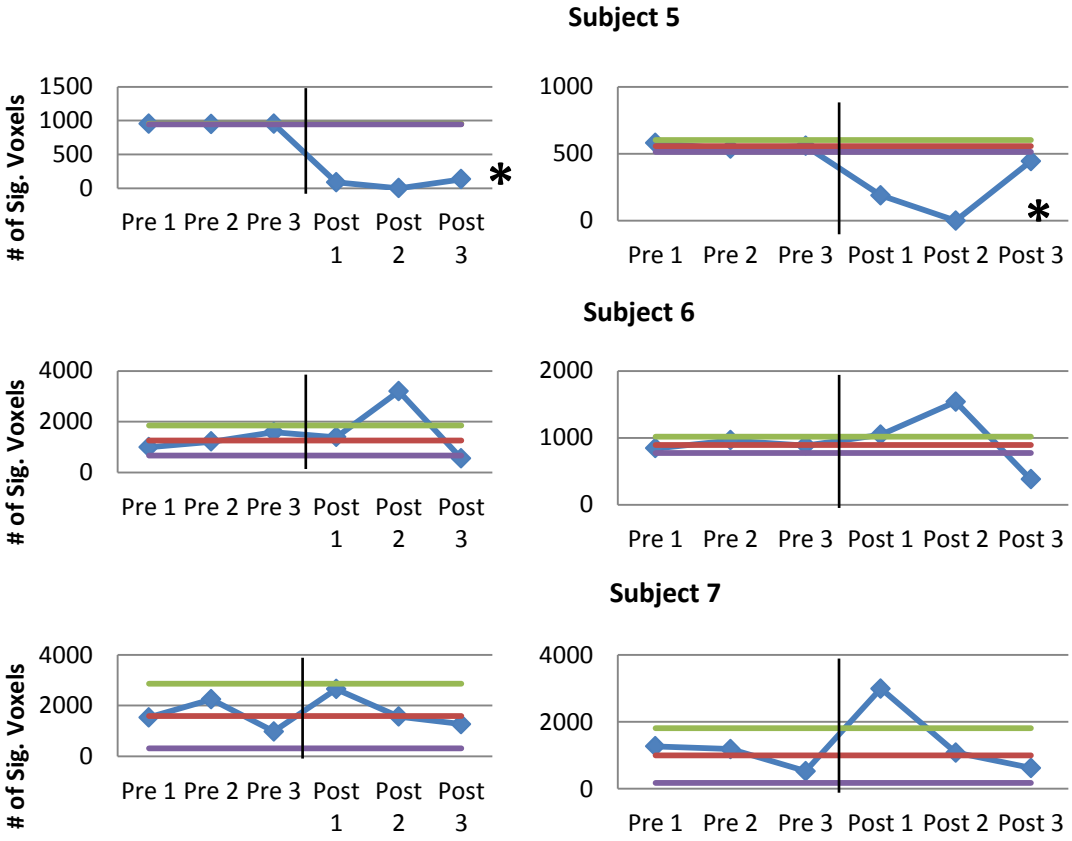


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 18: 2-Back PCC Voxel Count

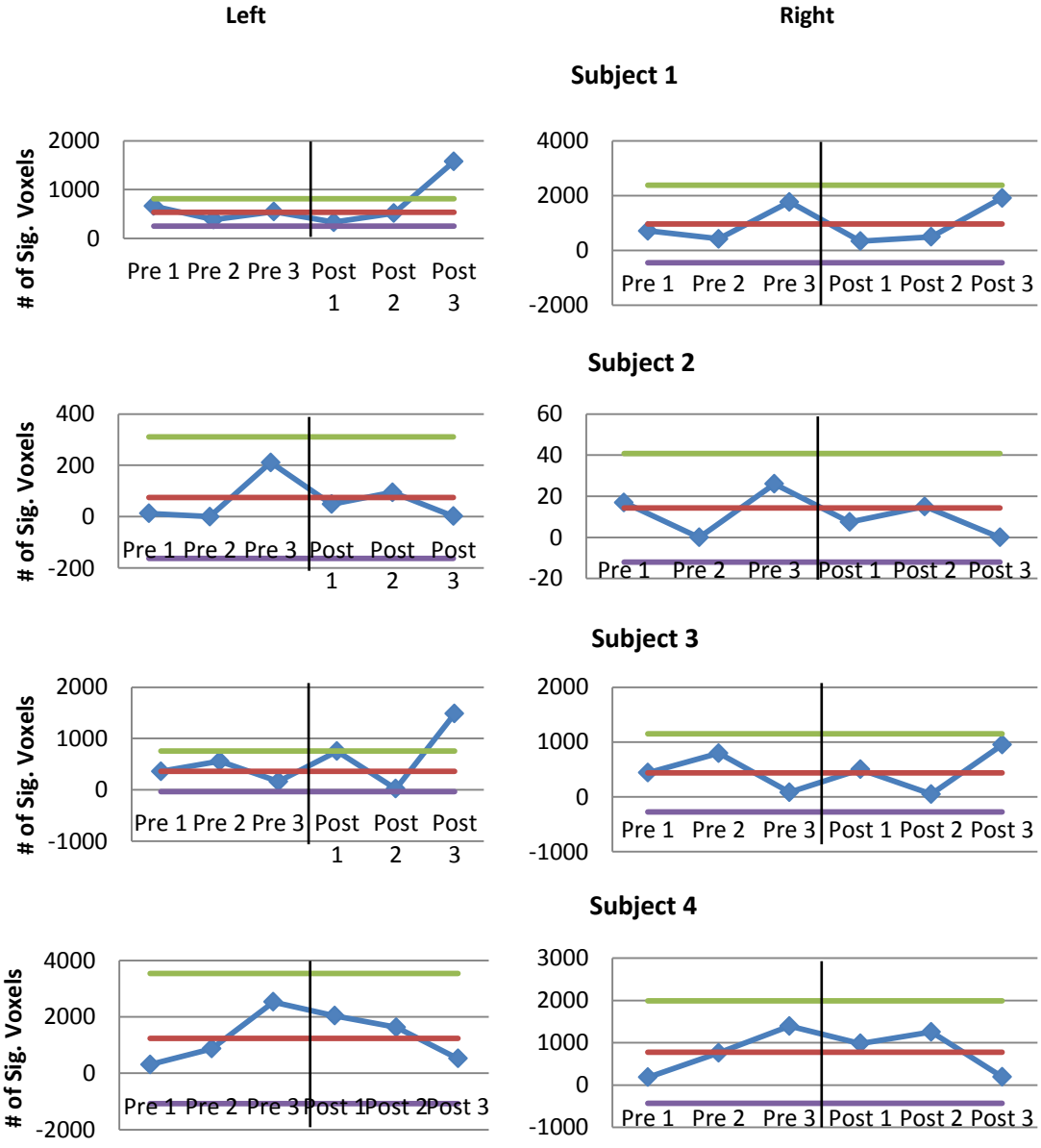


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

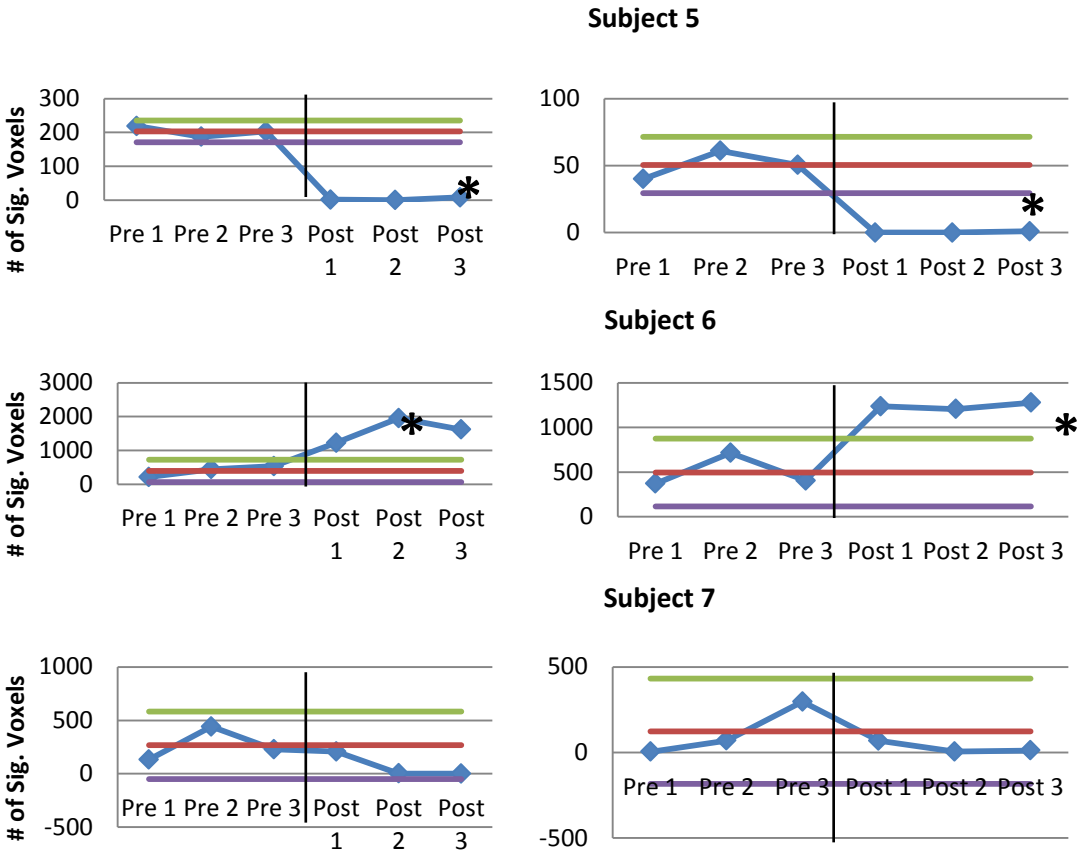


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Apppendix 18: -0+2 Back PCC Voxel Count

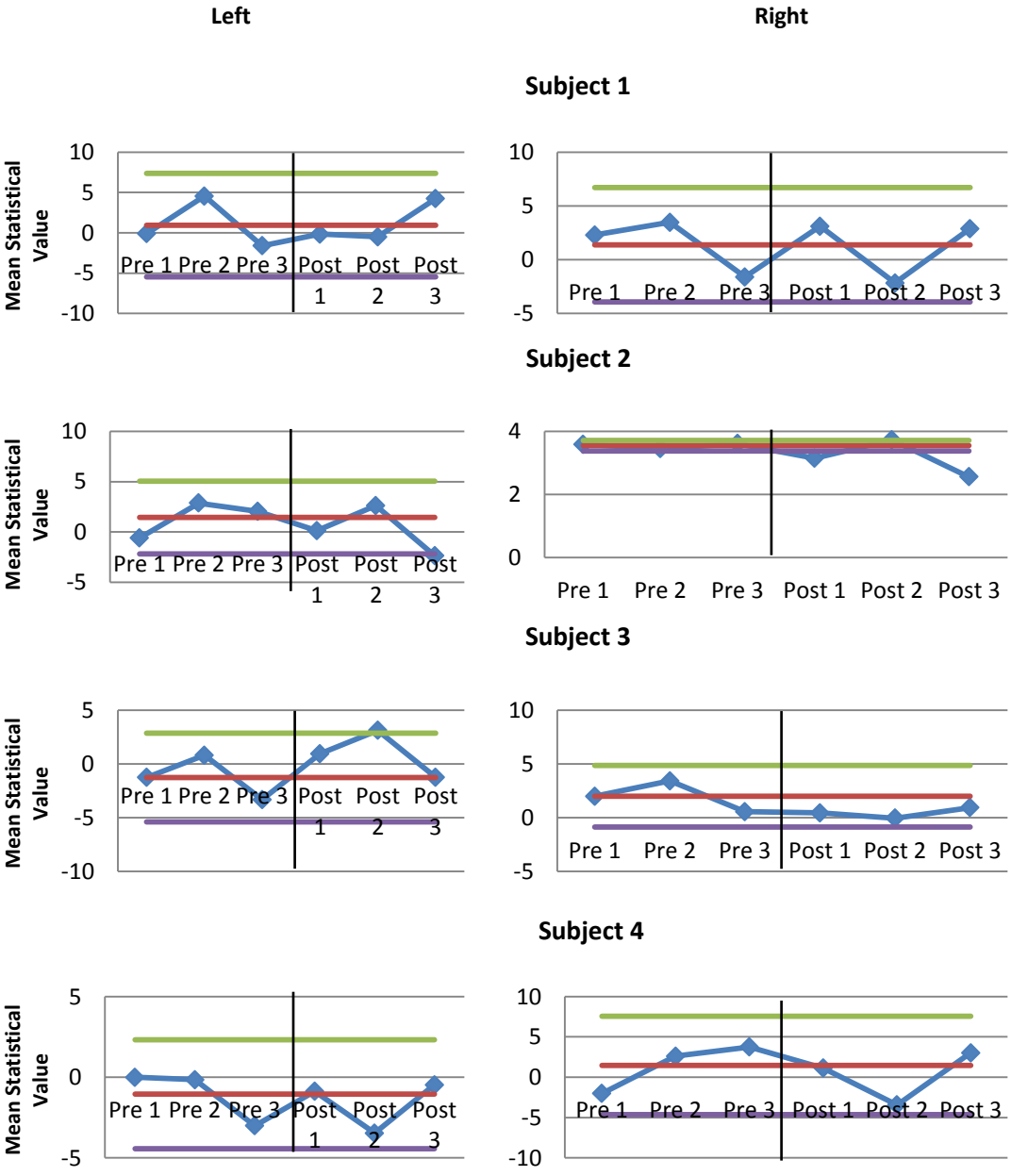


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

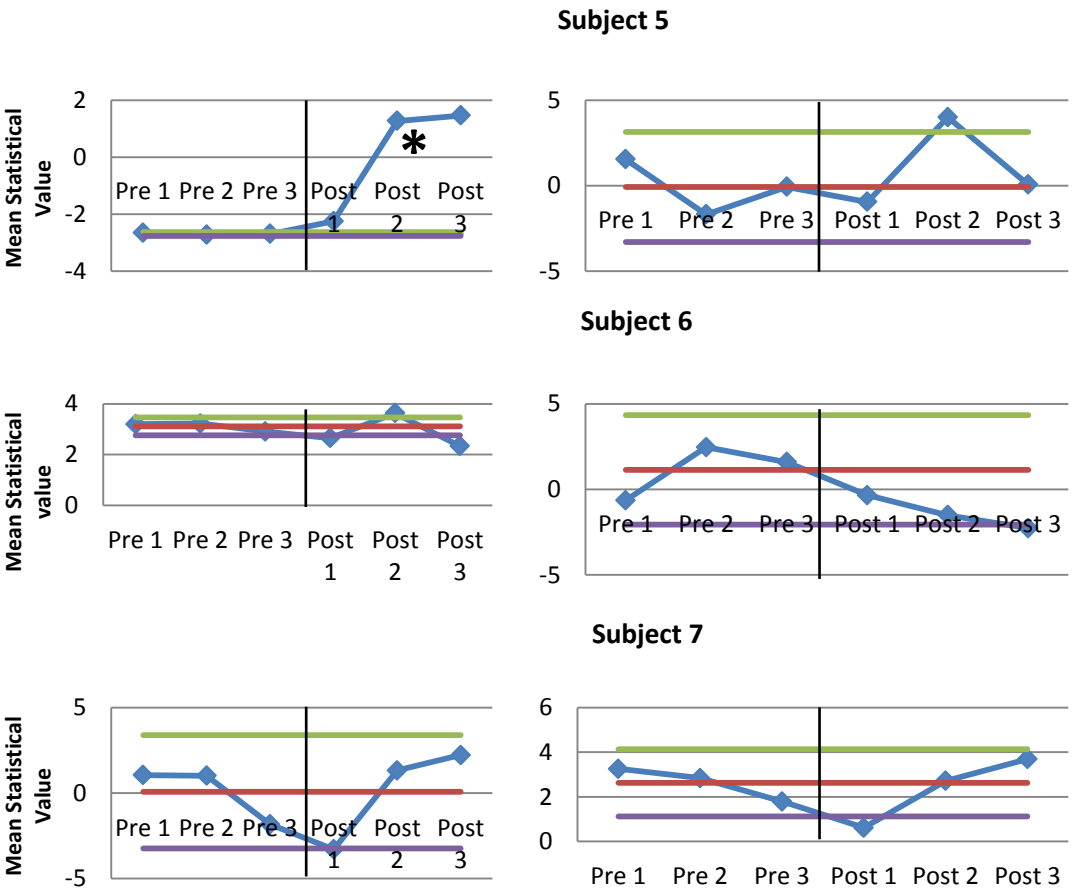


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 19: 0-Back DLPFC Intensity

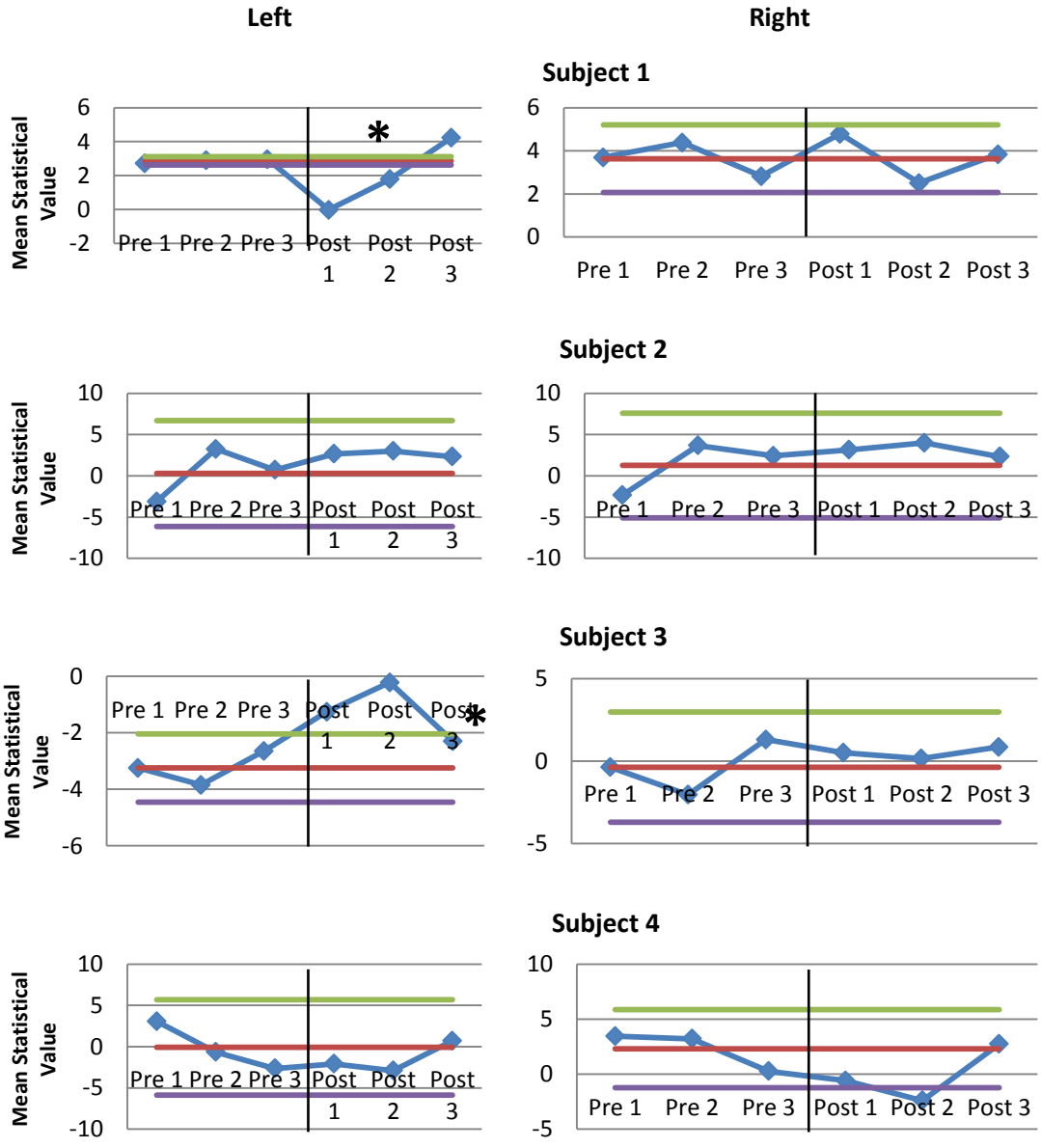


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

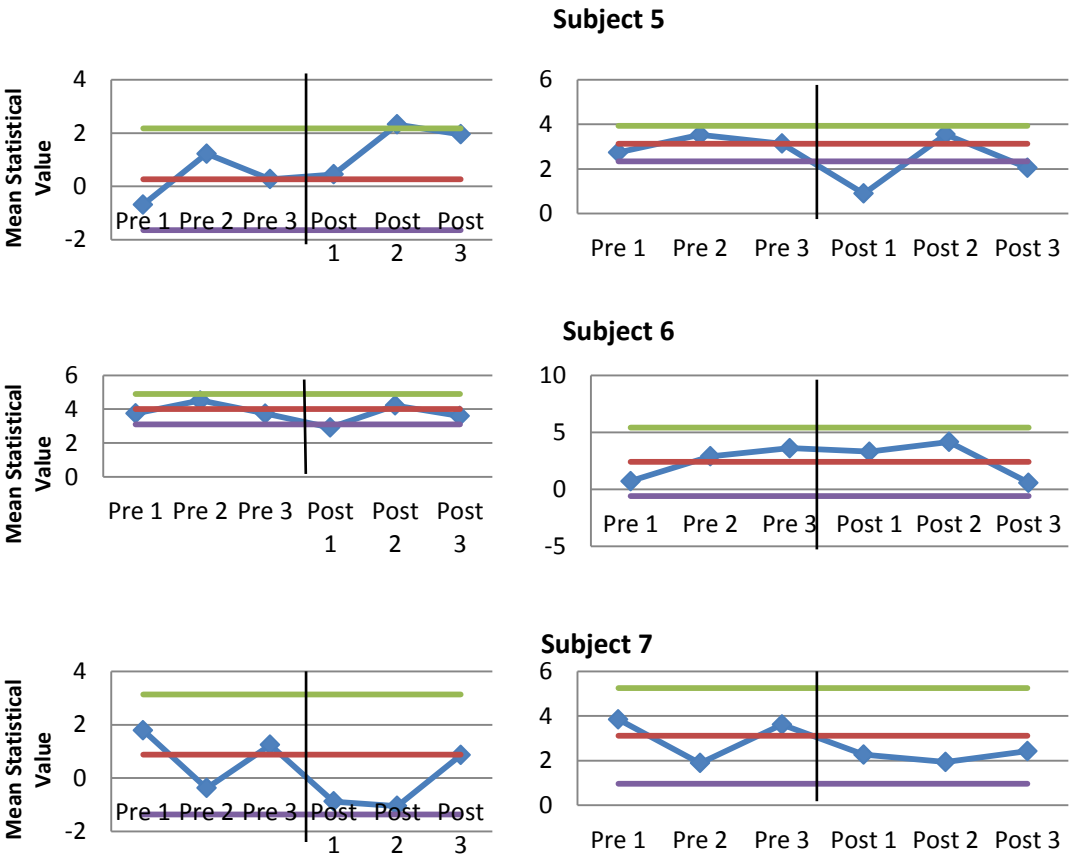


Upper bold line indicates 2SD above mean; Center bold line indicates mean
Lower bold line indicates 2SD below mean; Vertical bold line indicates aerobic intervention

Appendix 19: 2 Back DLPFC Intensity

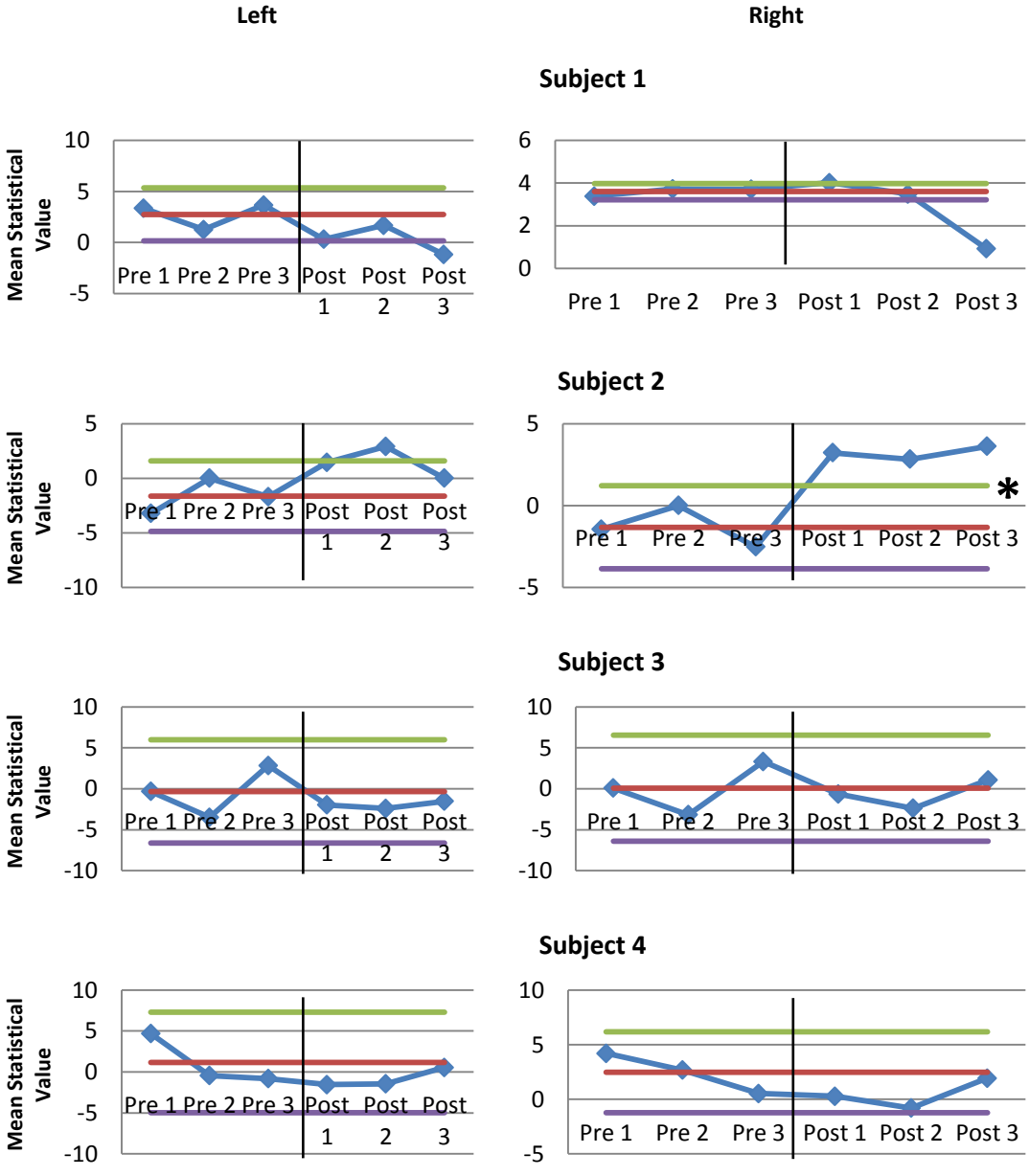


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

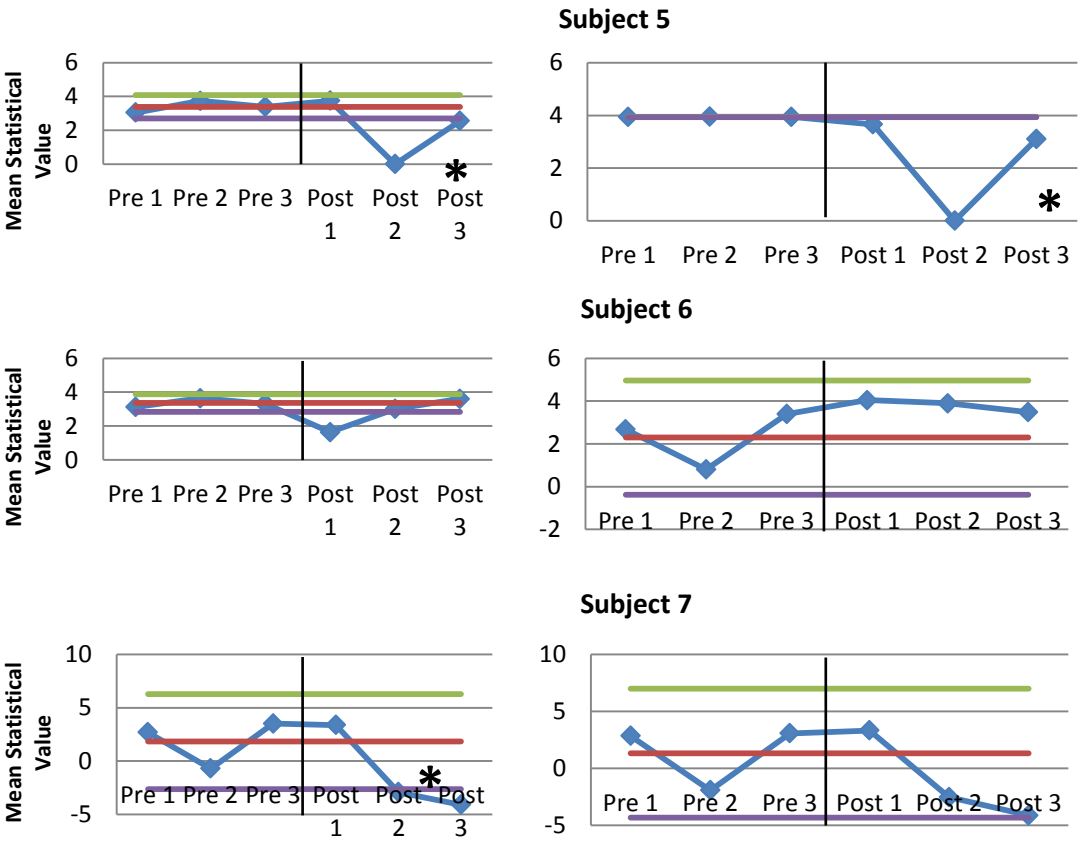


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 19: -0+2-Back DLPFC Intensity

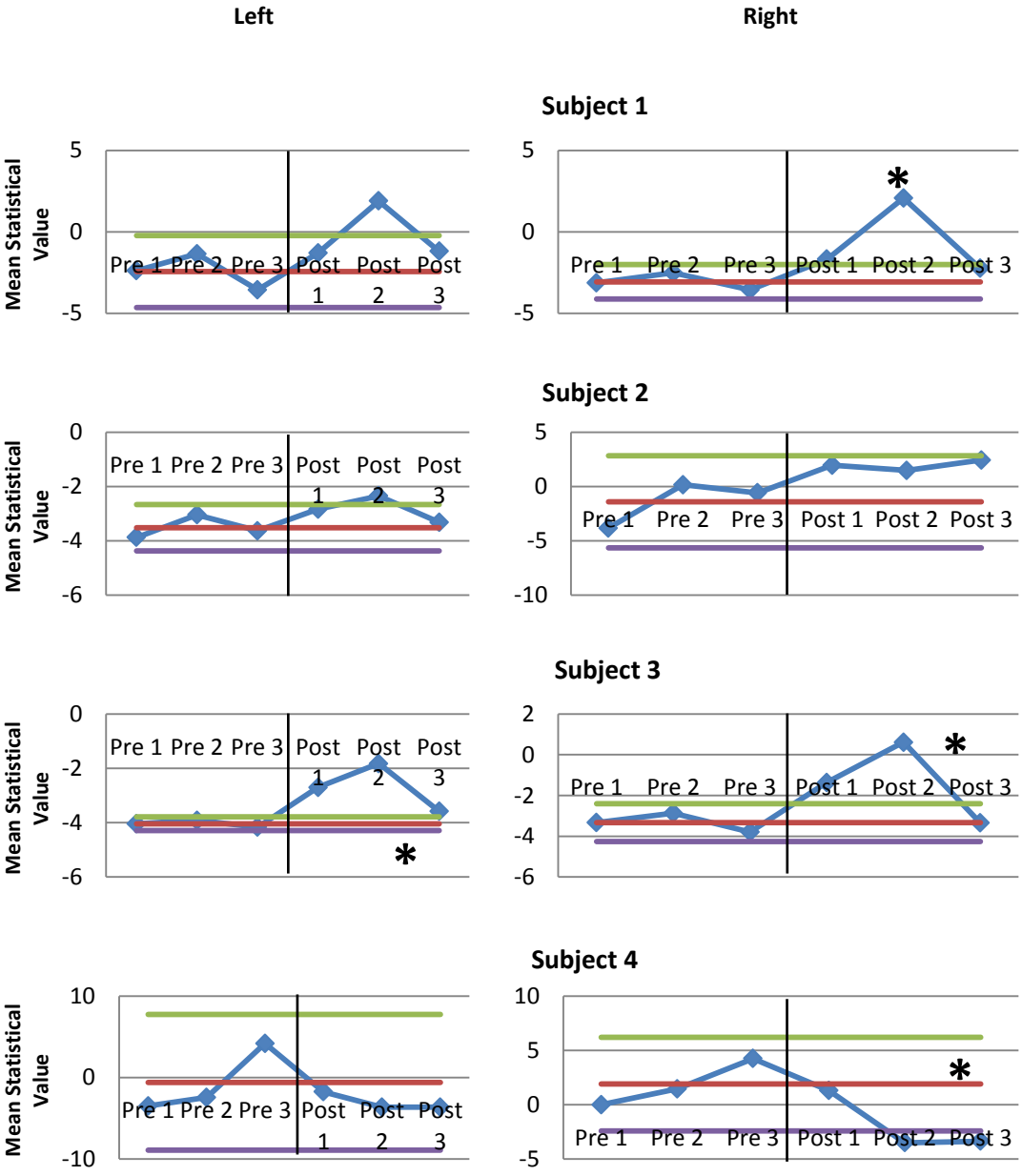


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

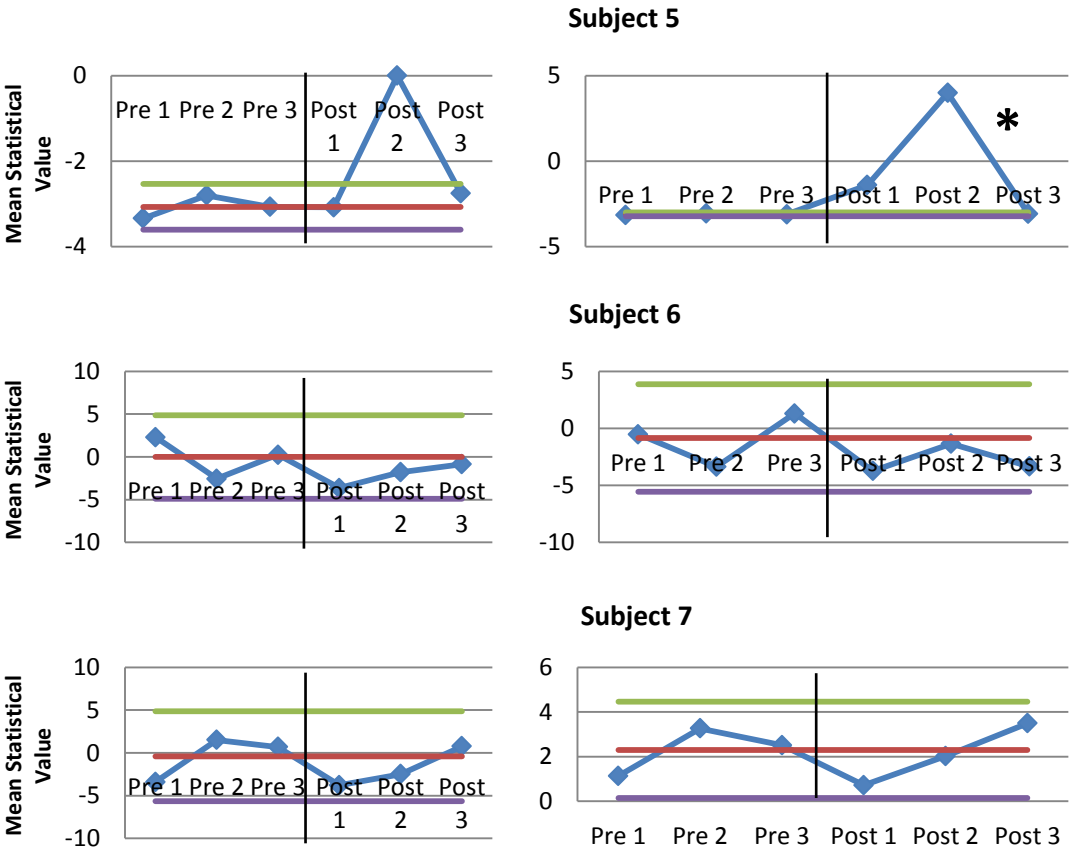


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SC below mean; Vertical bold line indicates aerobic intervention

Appendix 20: 0-Back Precuneus Intensity

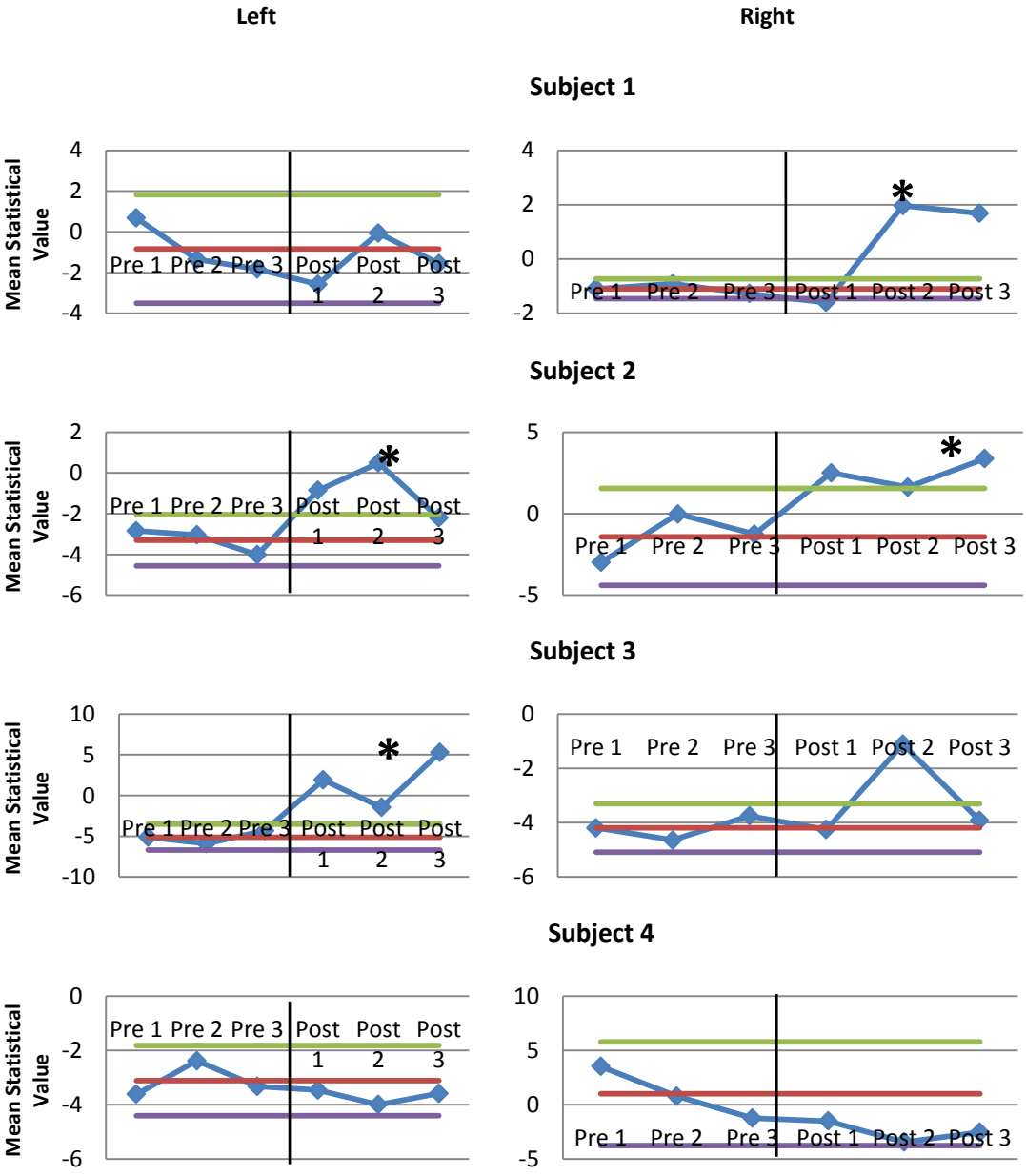


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

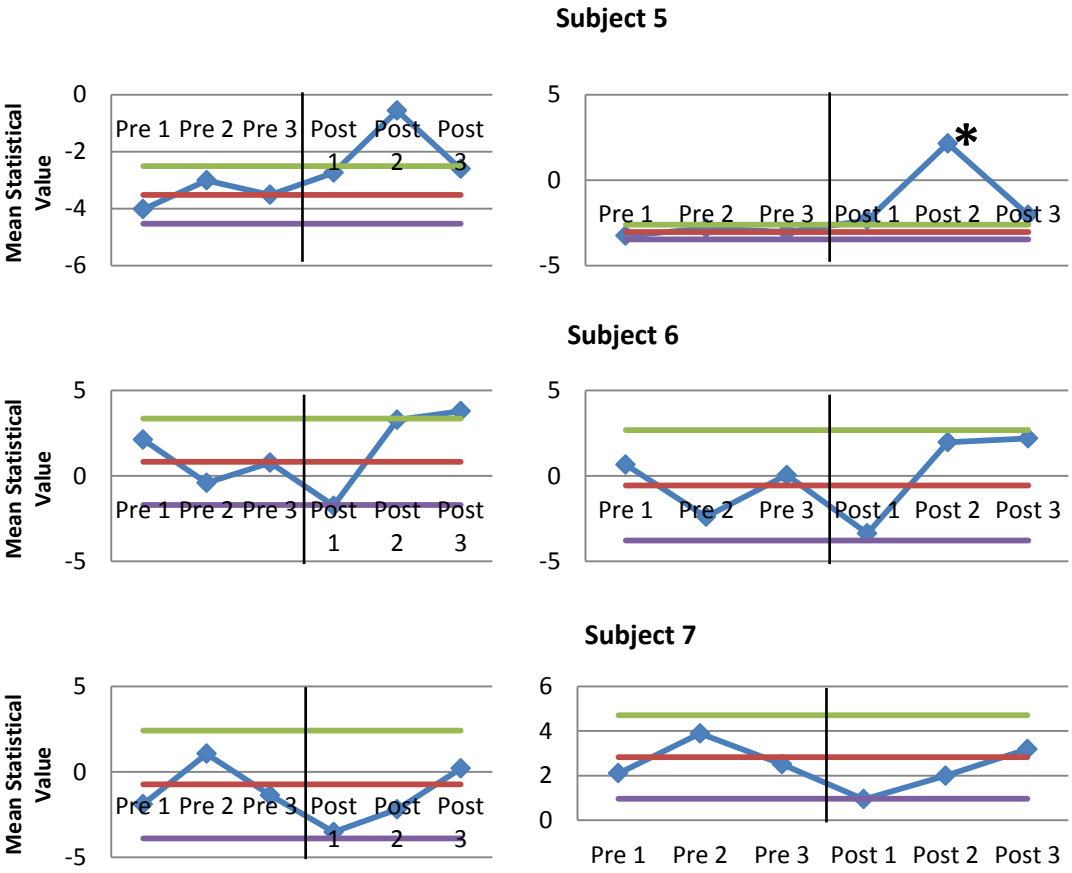


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 20: 2-Back Precuneus Intensity



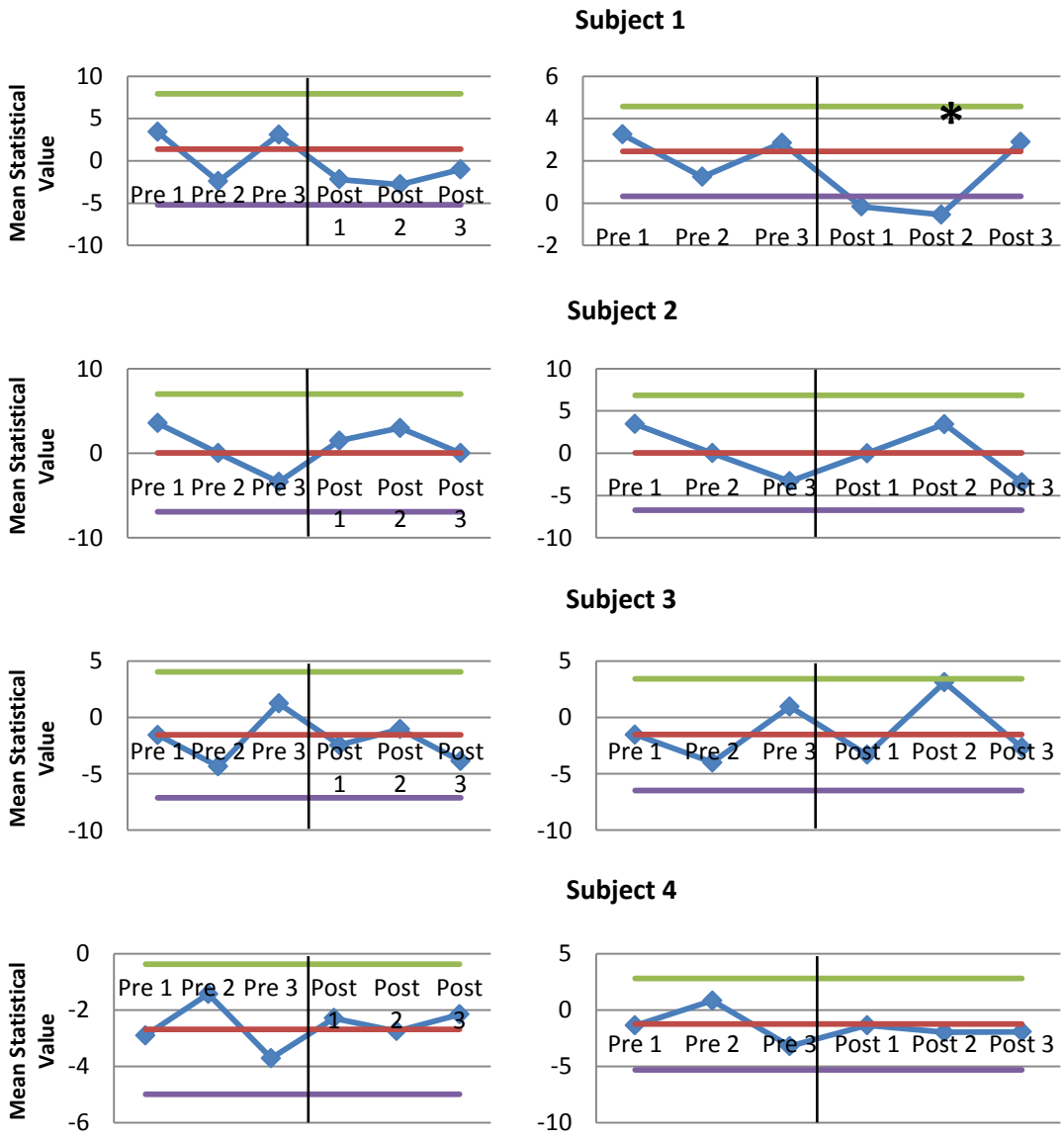
Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention



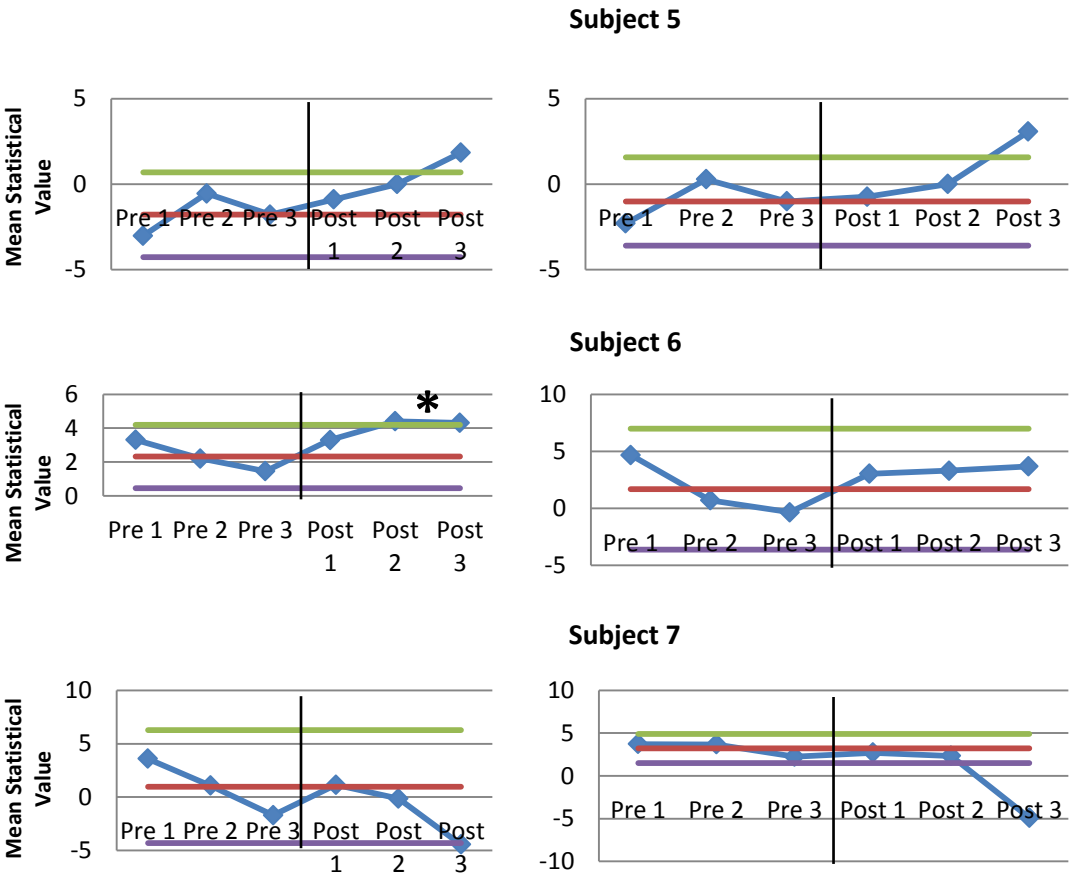
Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 20: -0+2-Back Precuneus Intensity

Left **Right**

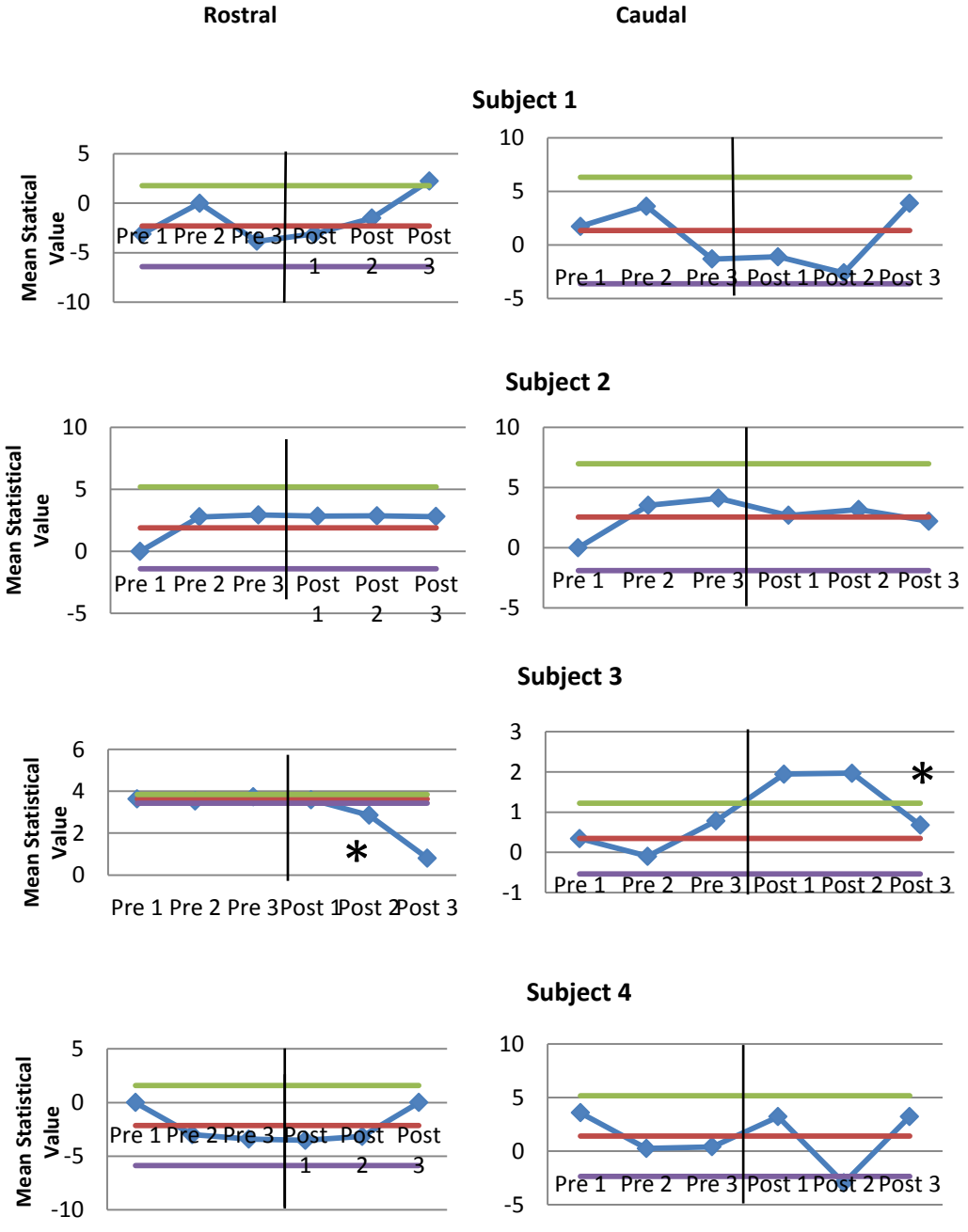


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

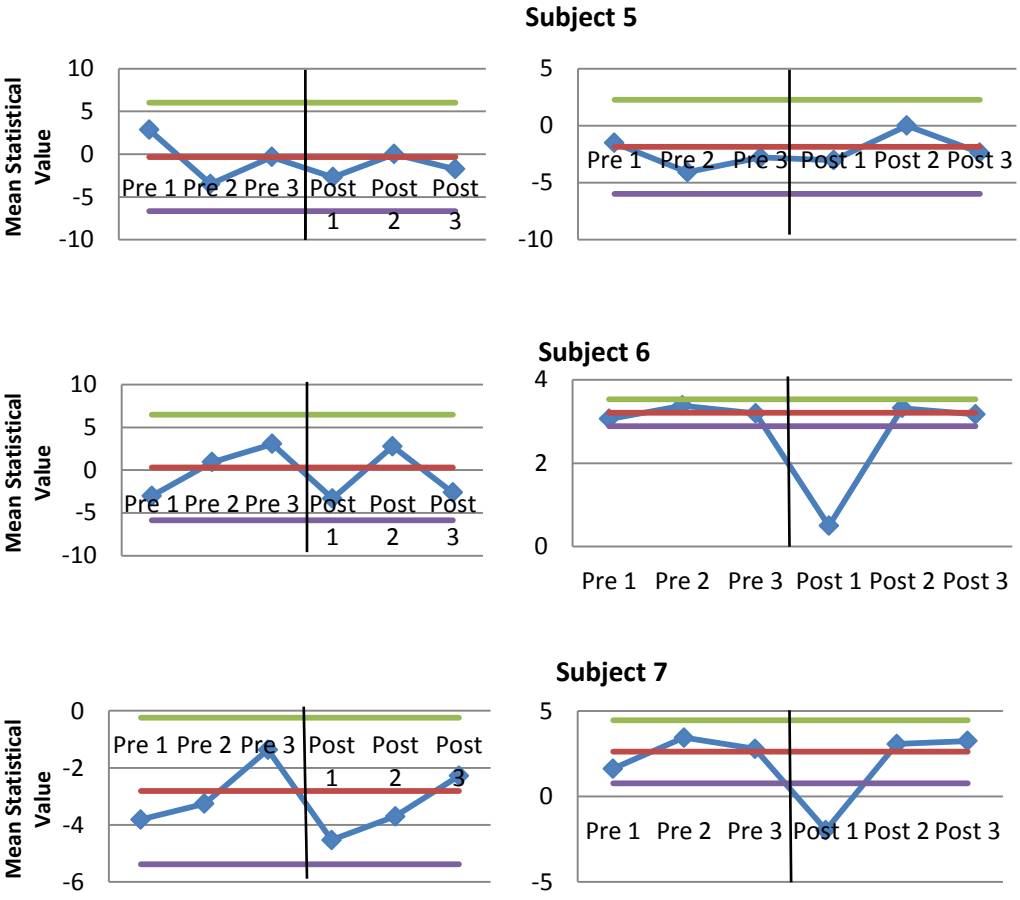


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 21: 0-Back ACC Intensity

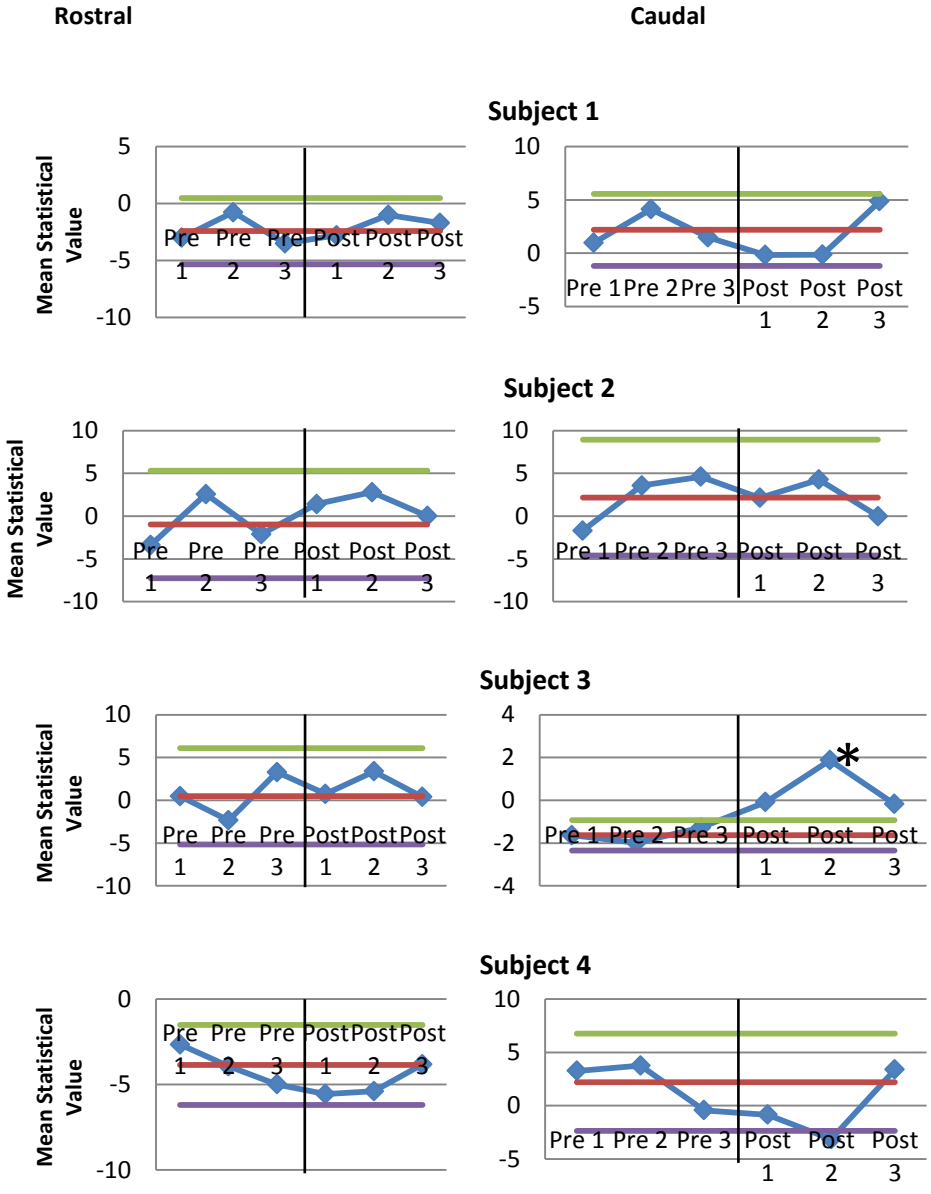


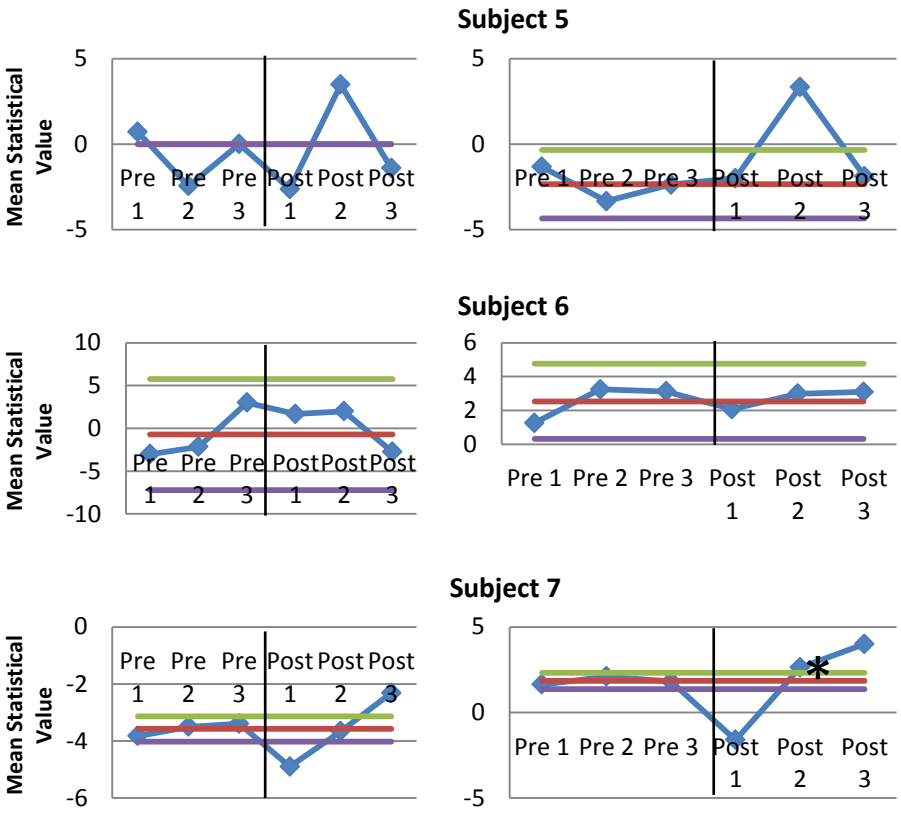
Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention



Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

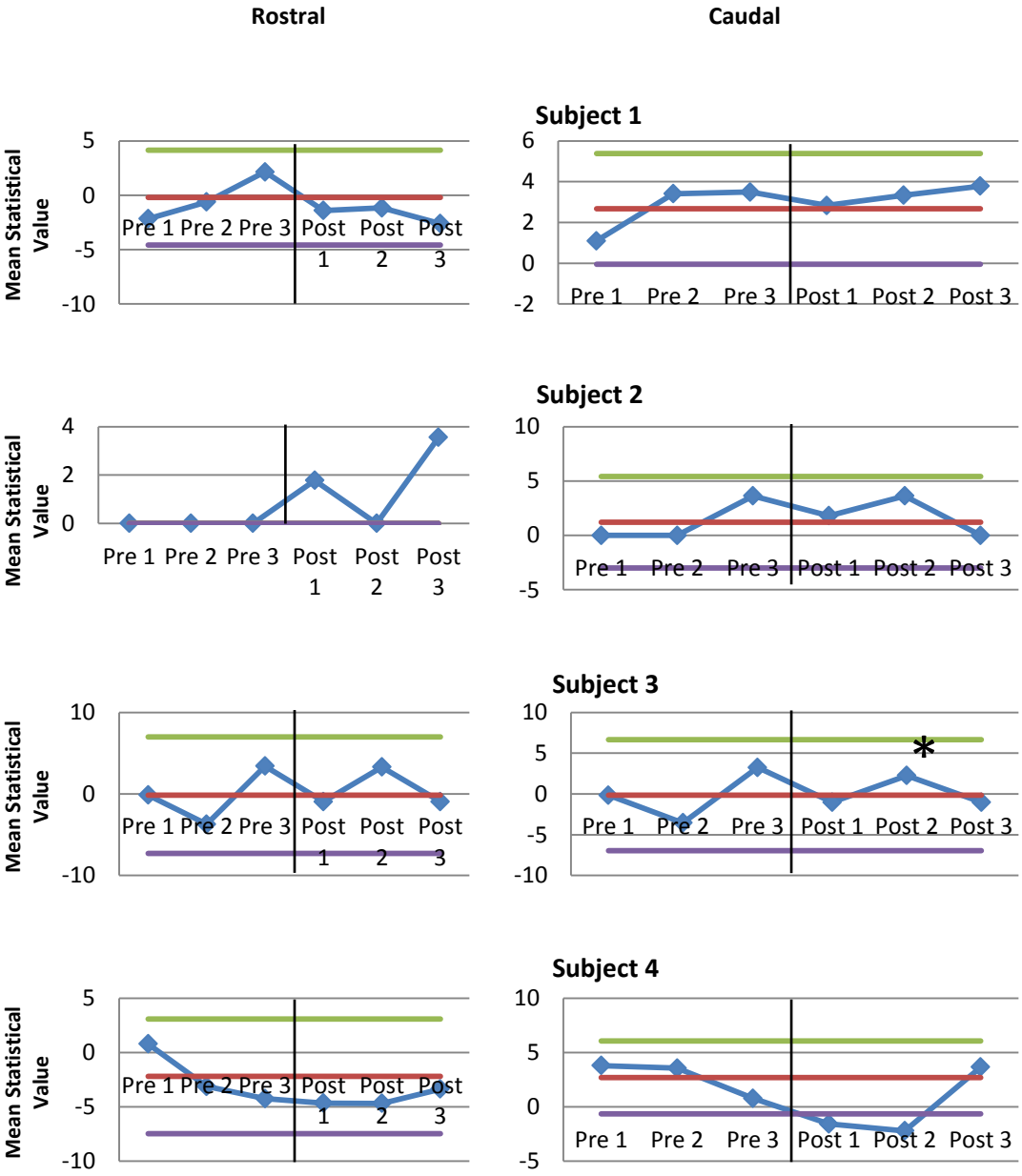
Appendix 21: 2-Back ACC Intensity



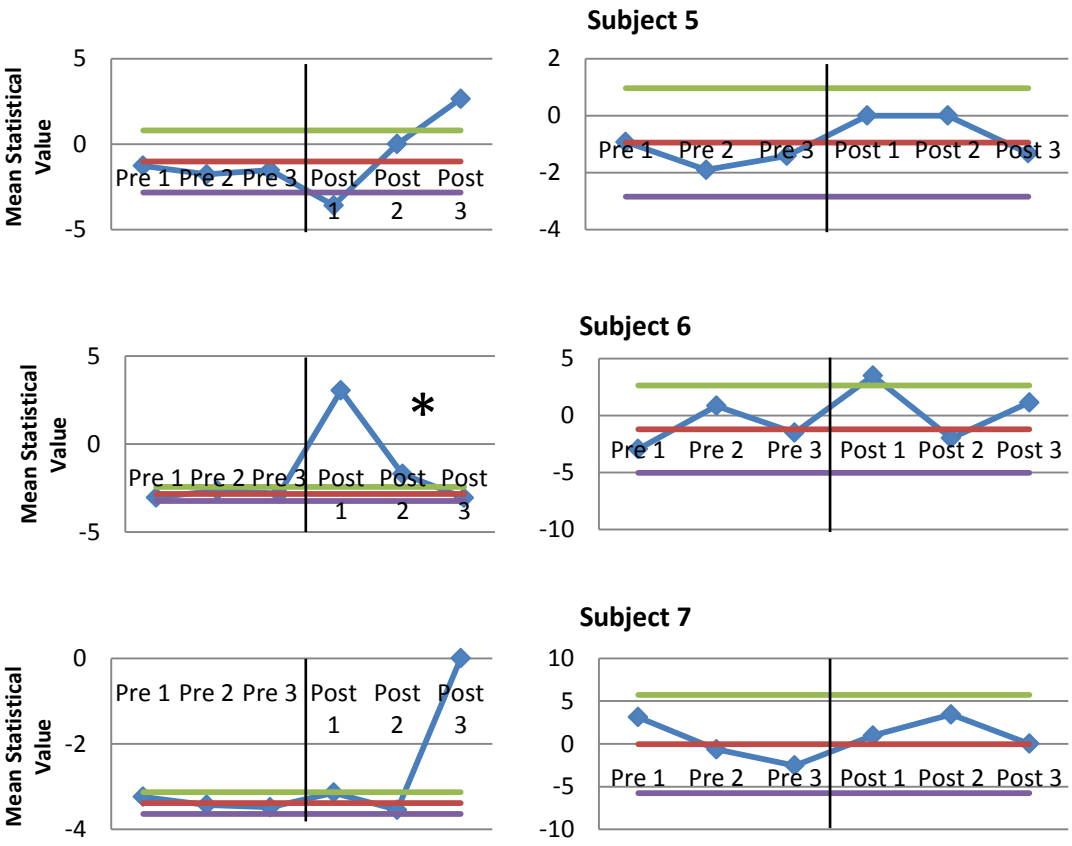


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 21: -0+2 Back ACC Intensity

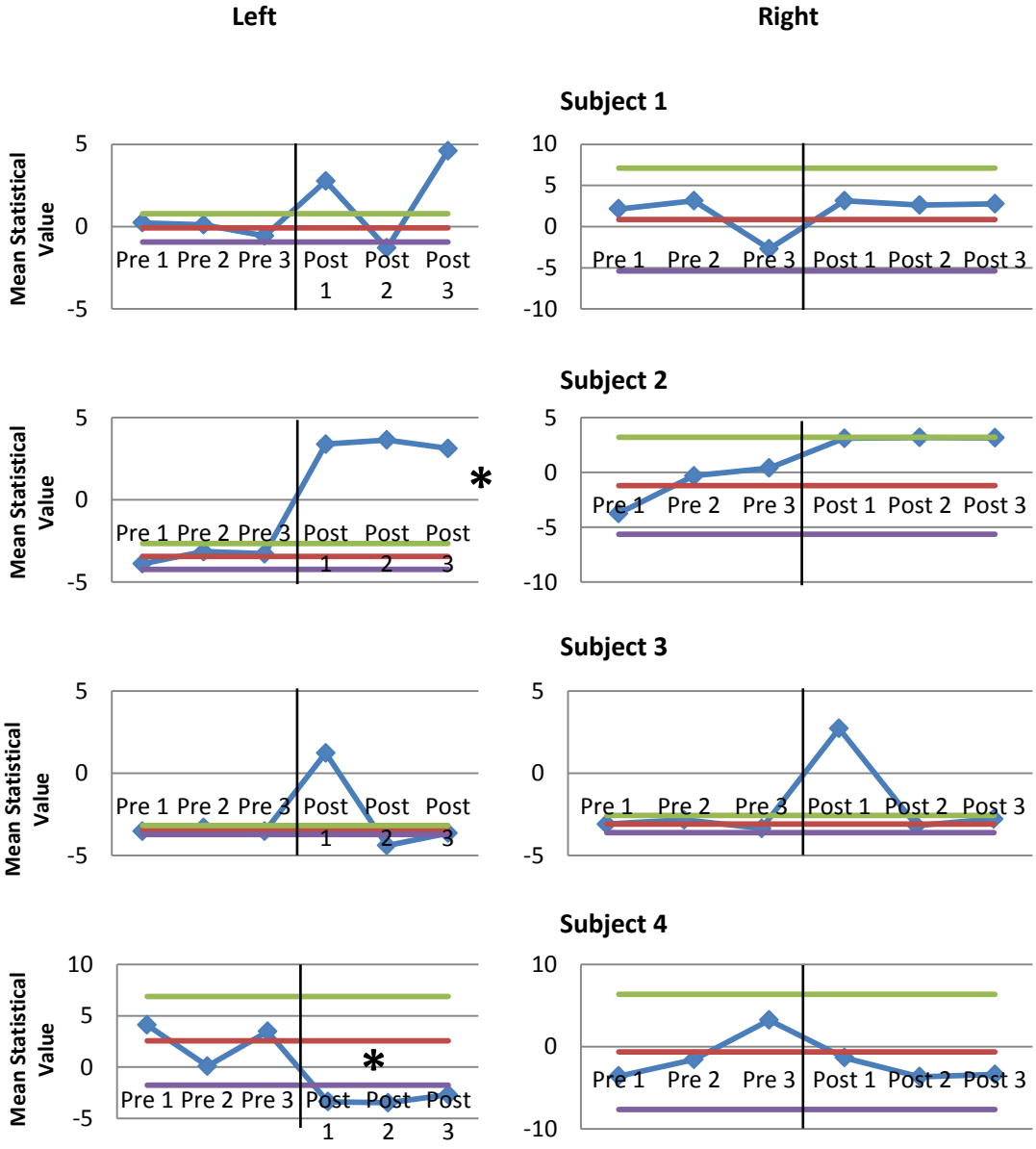


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

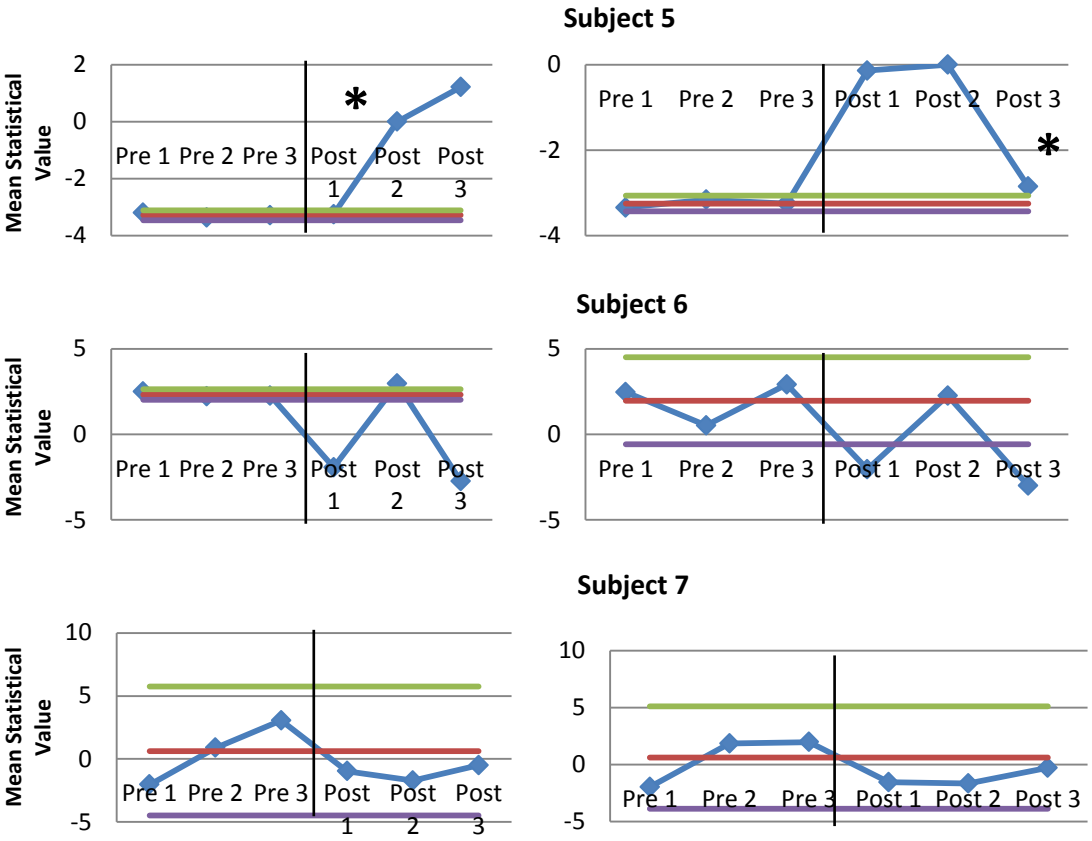


Upper bold line indicates 2 SD above mean; Middle bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 22: 0-Back PCC Intensity

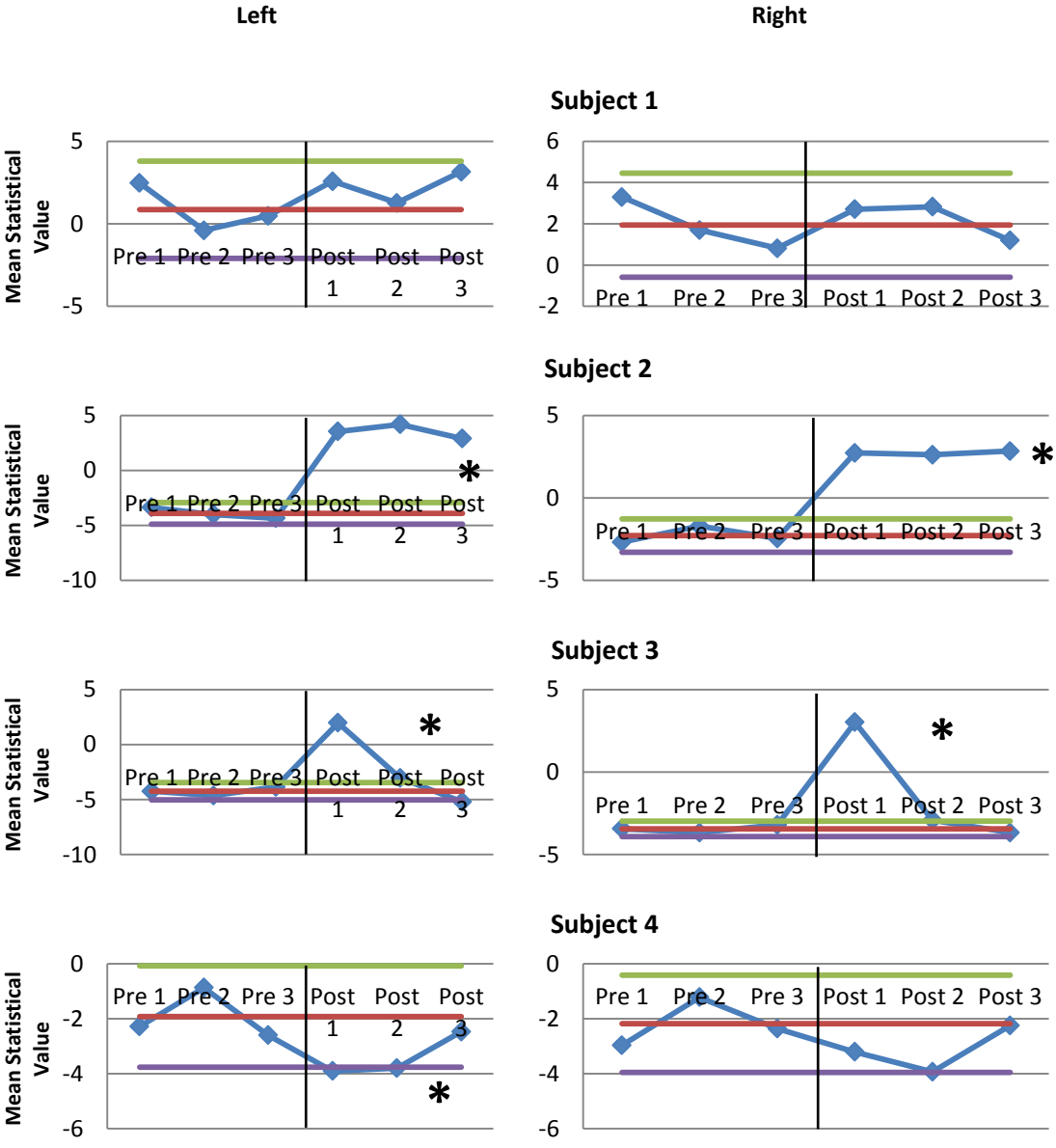


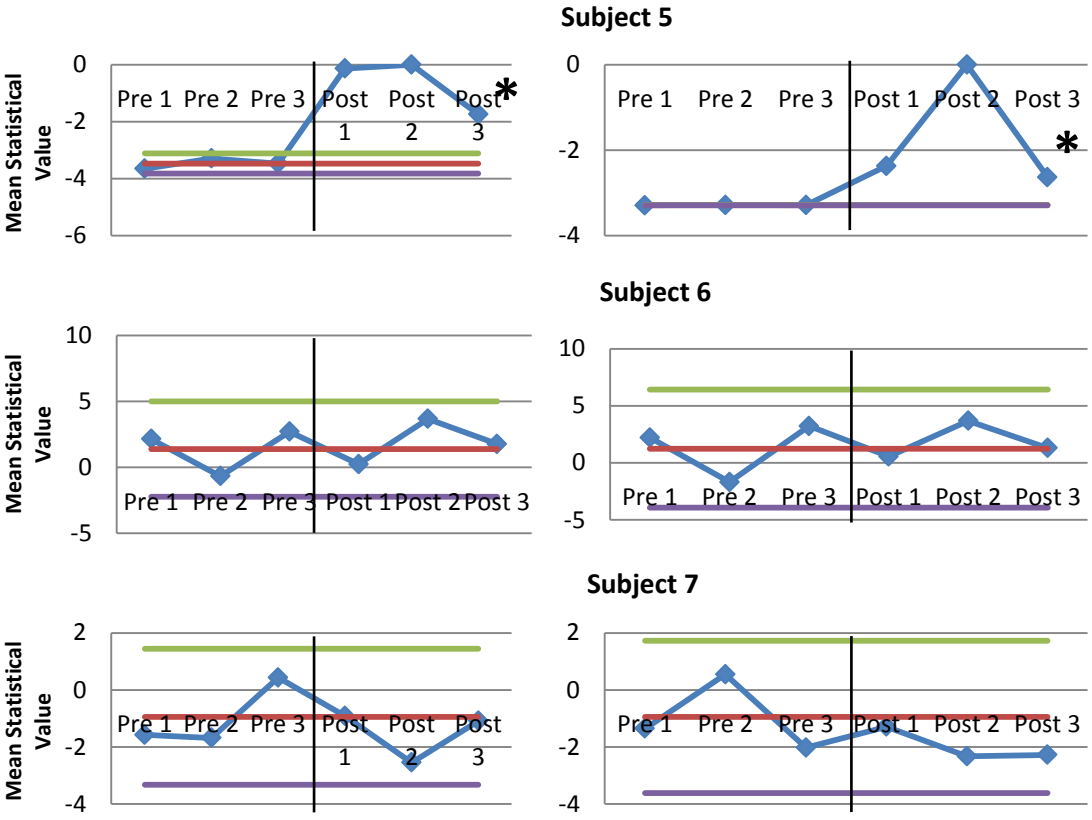
Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention



Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

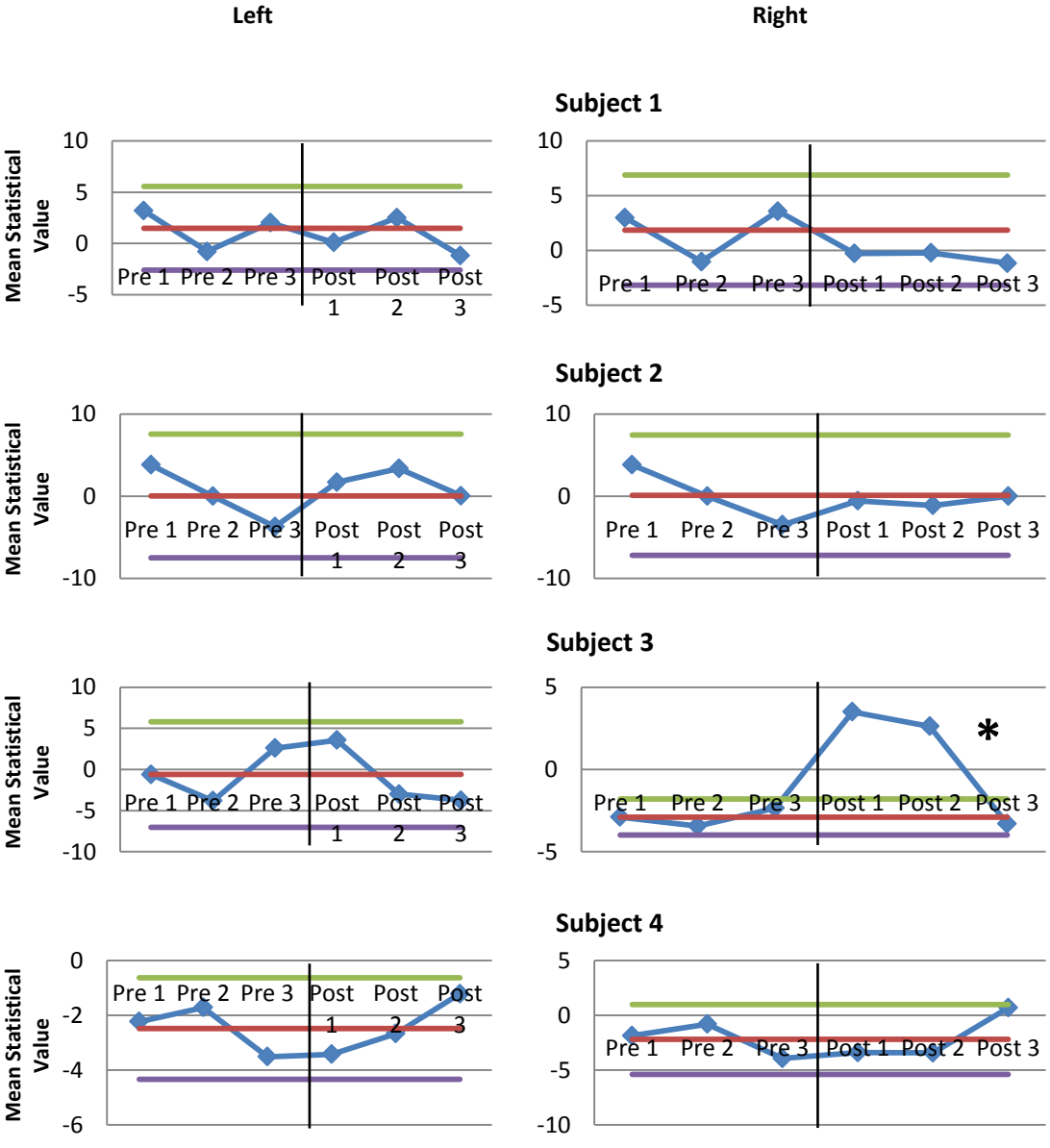
Appendix 22: 2-Back PCC Intensity

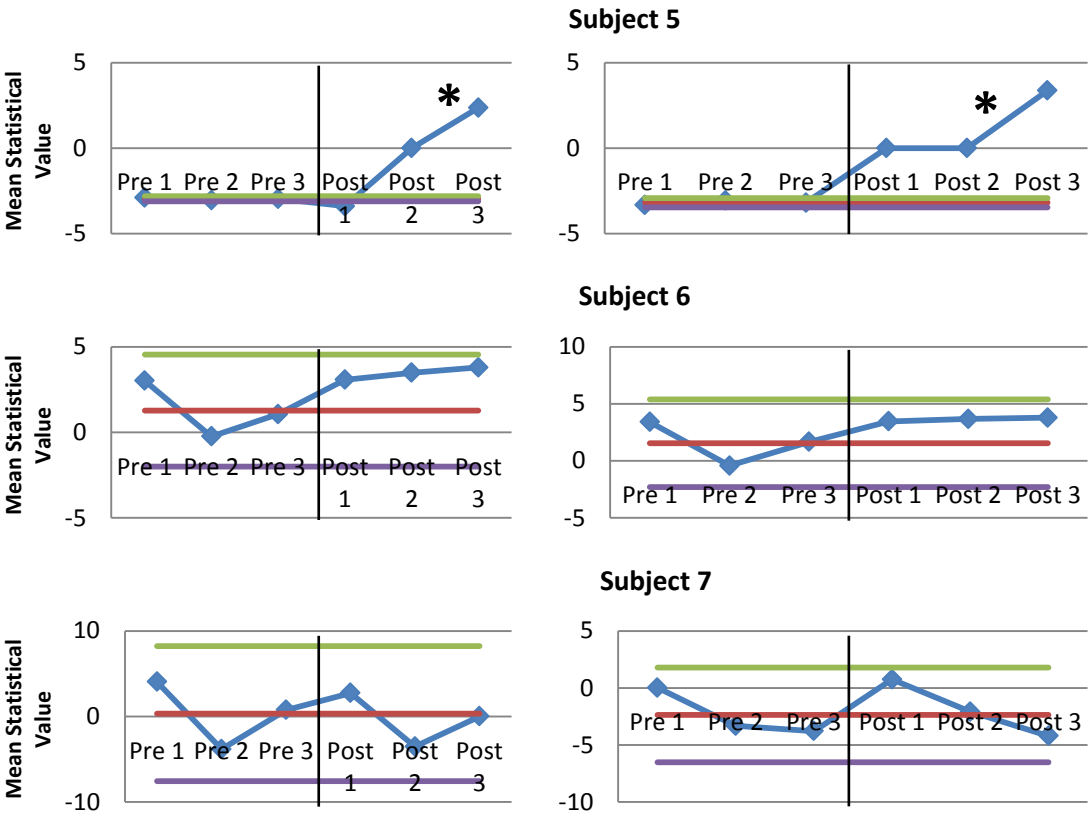




Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

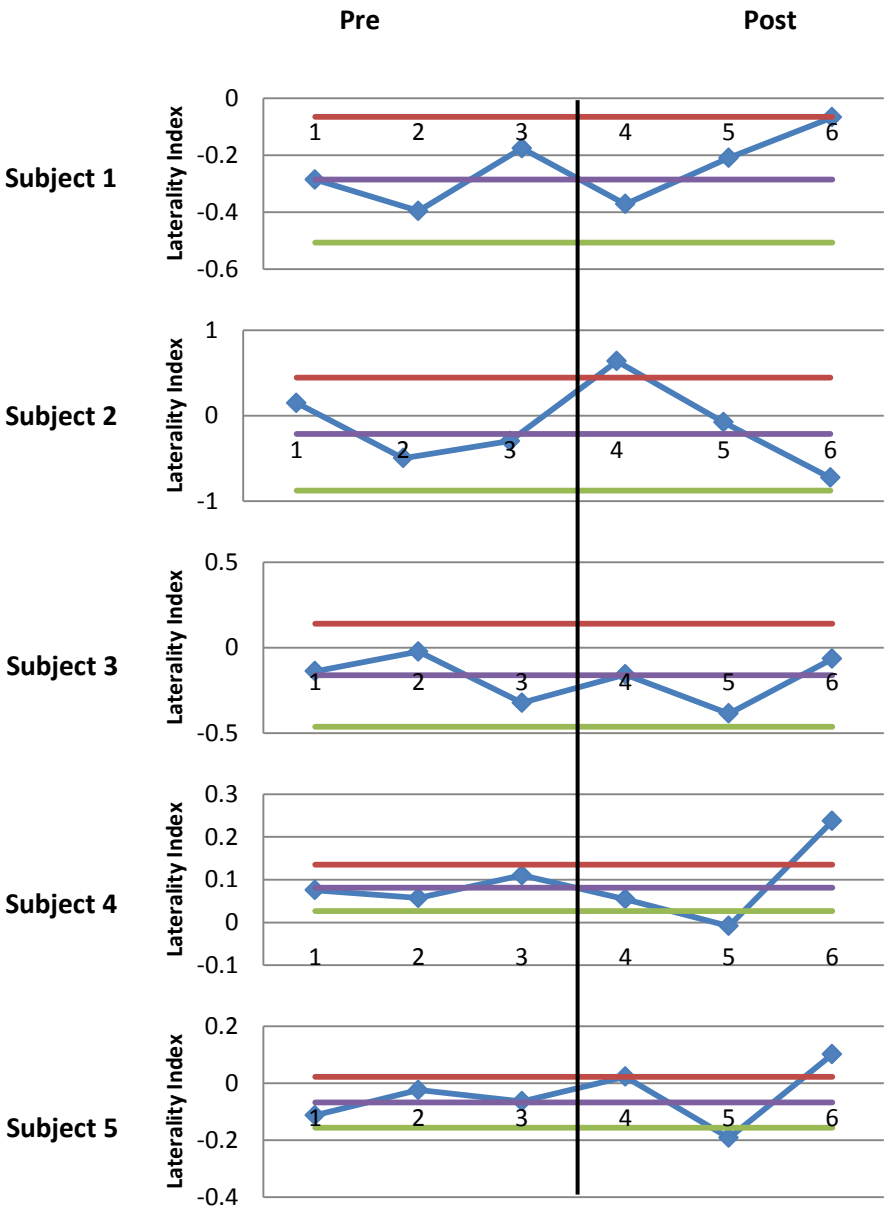
Appendix 22: -0+2-Back PCC Intensity

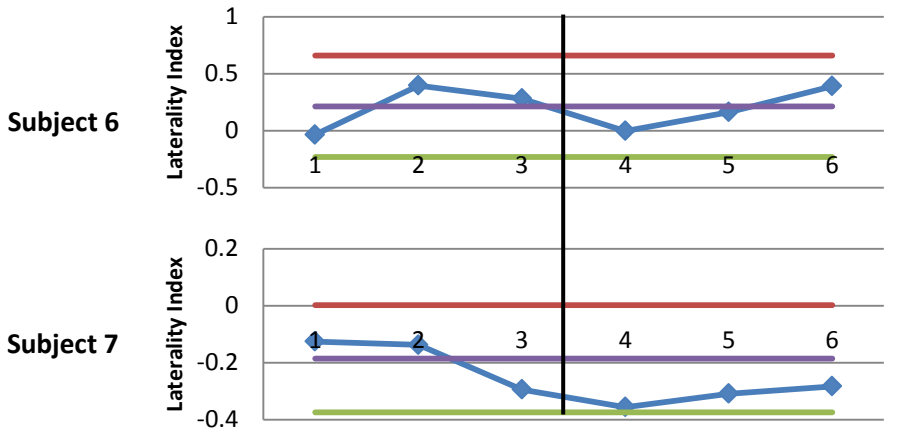




Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

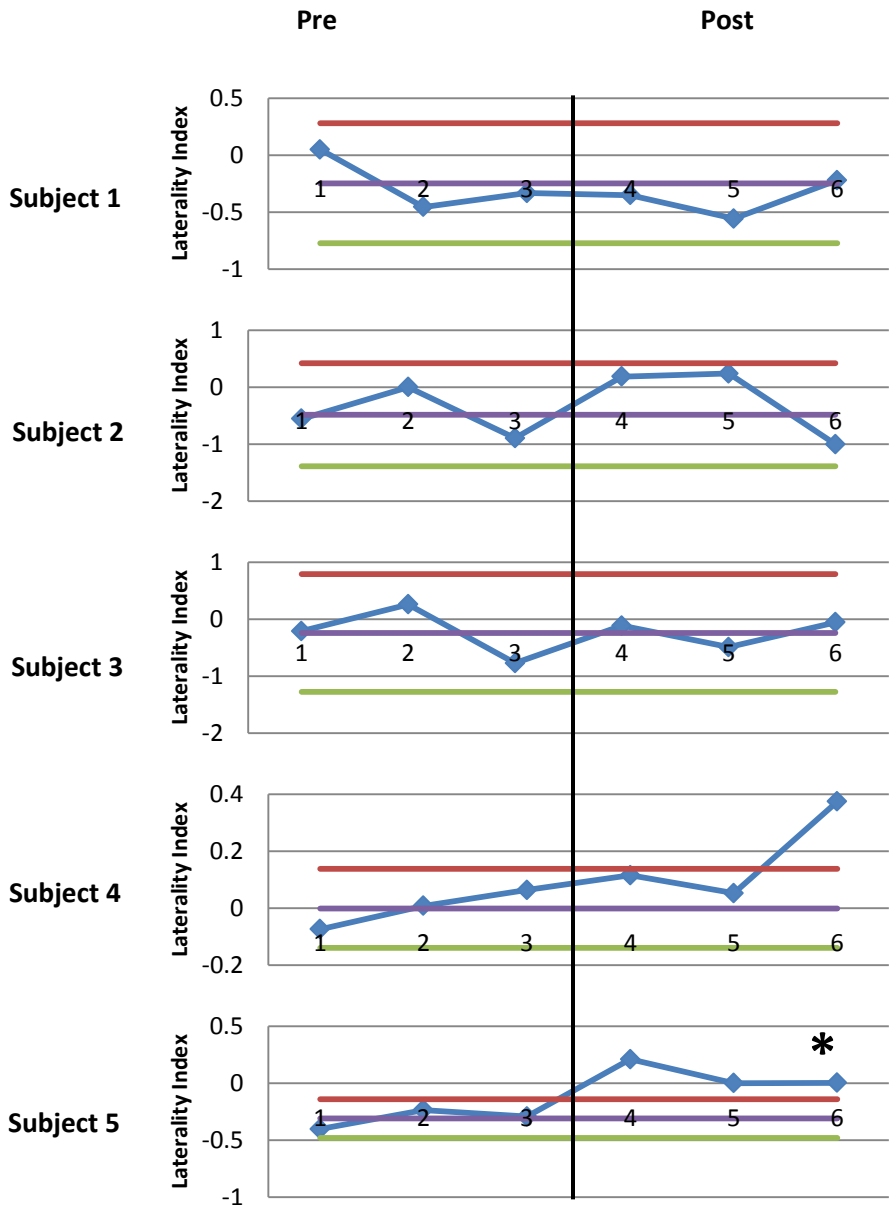
Appendix 23: DLPFC Laterality Index (2 Back)



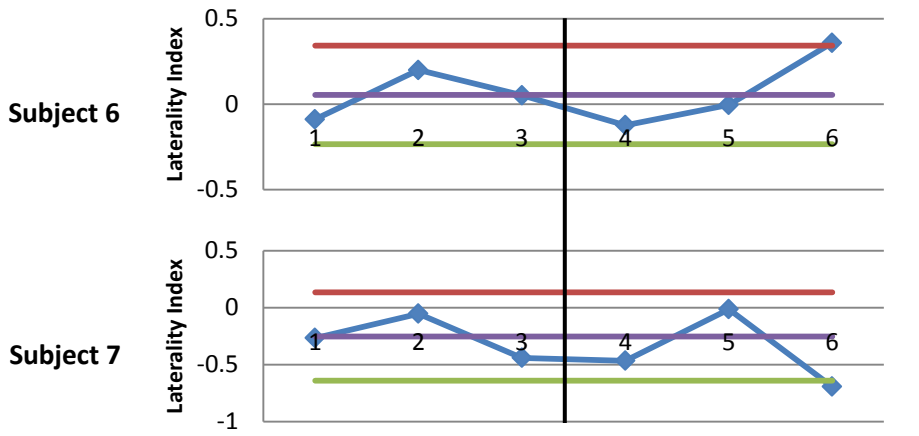


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 23: DLPFC Laterality Index (0+2 Back)

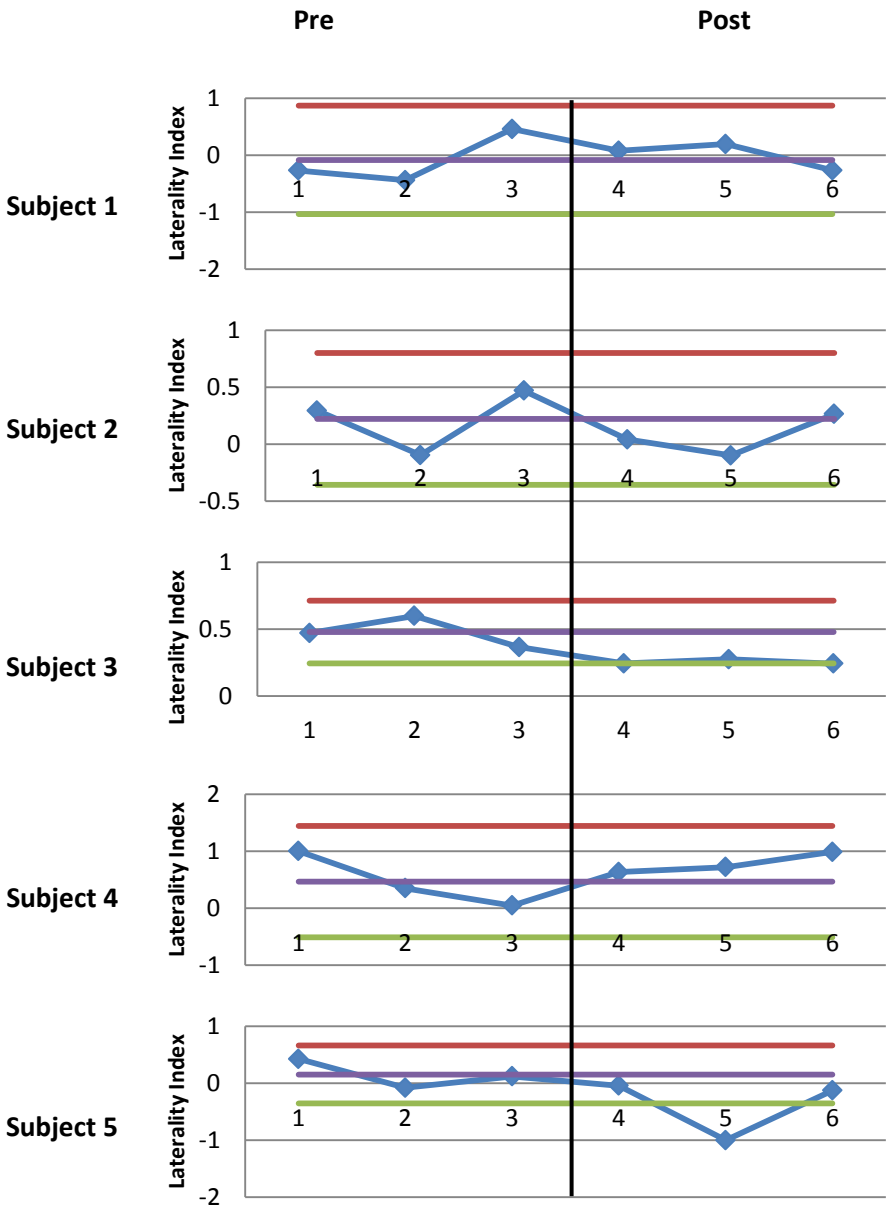


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

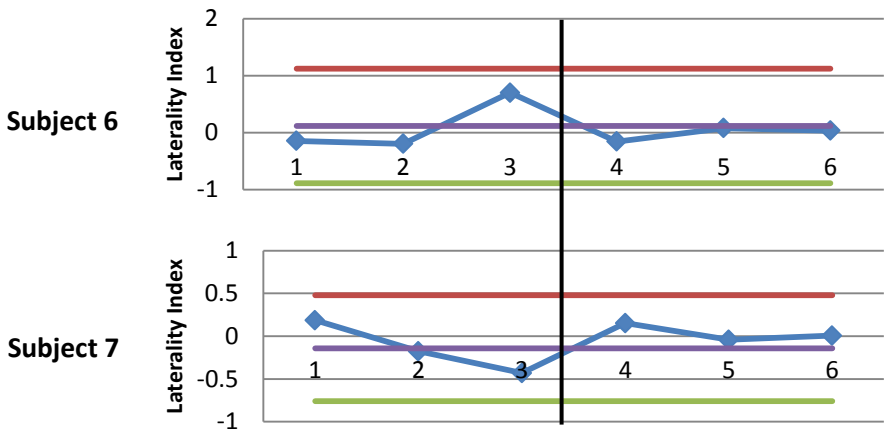


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 24: Precuneus Laterality Index (0 Back)

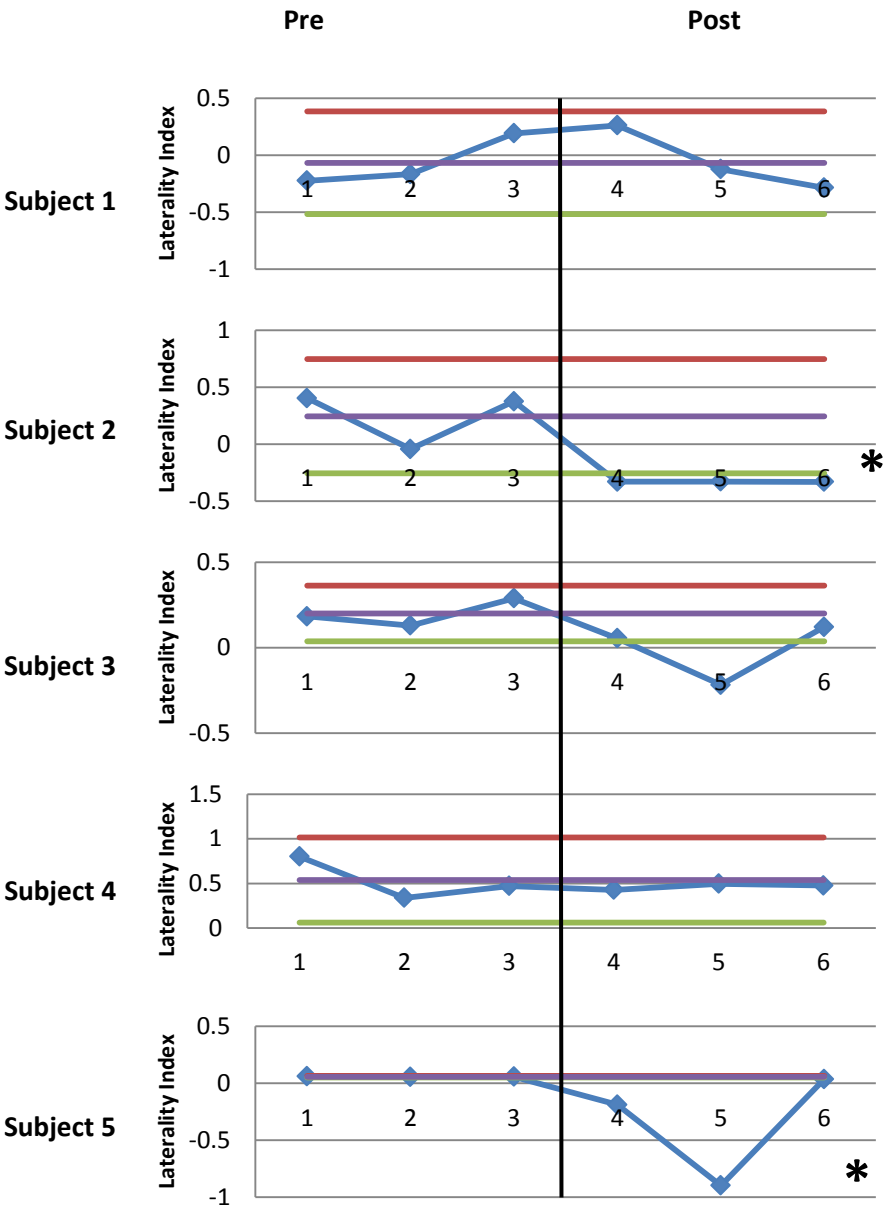


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

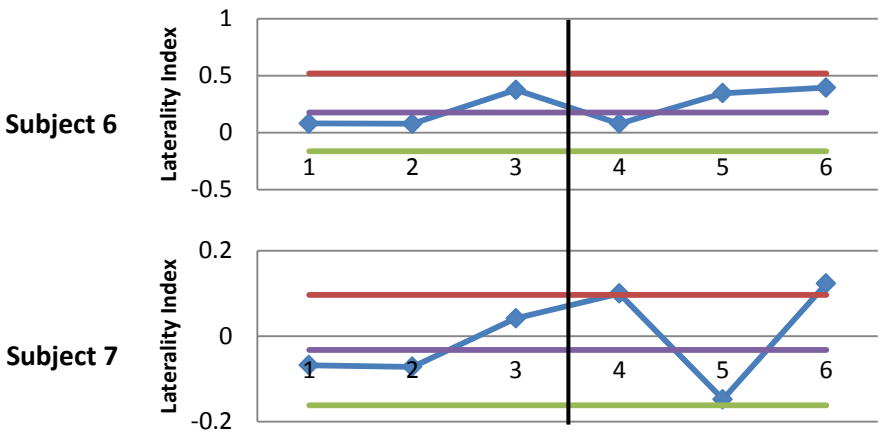


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 24: Precuneus Laterality Index (2 Back)

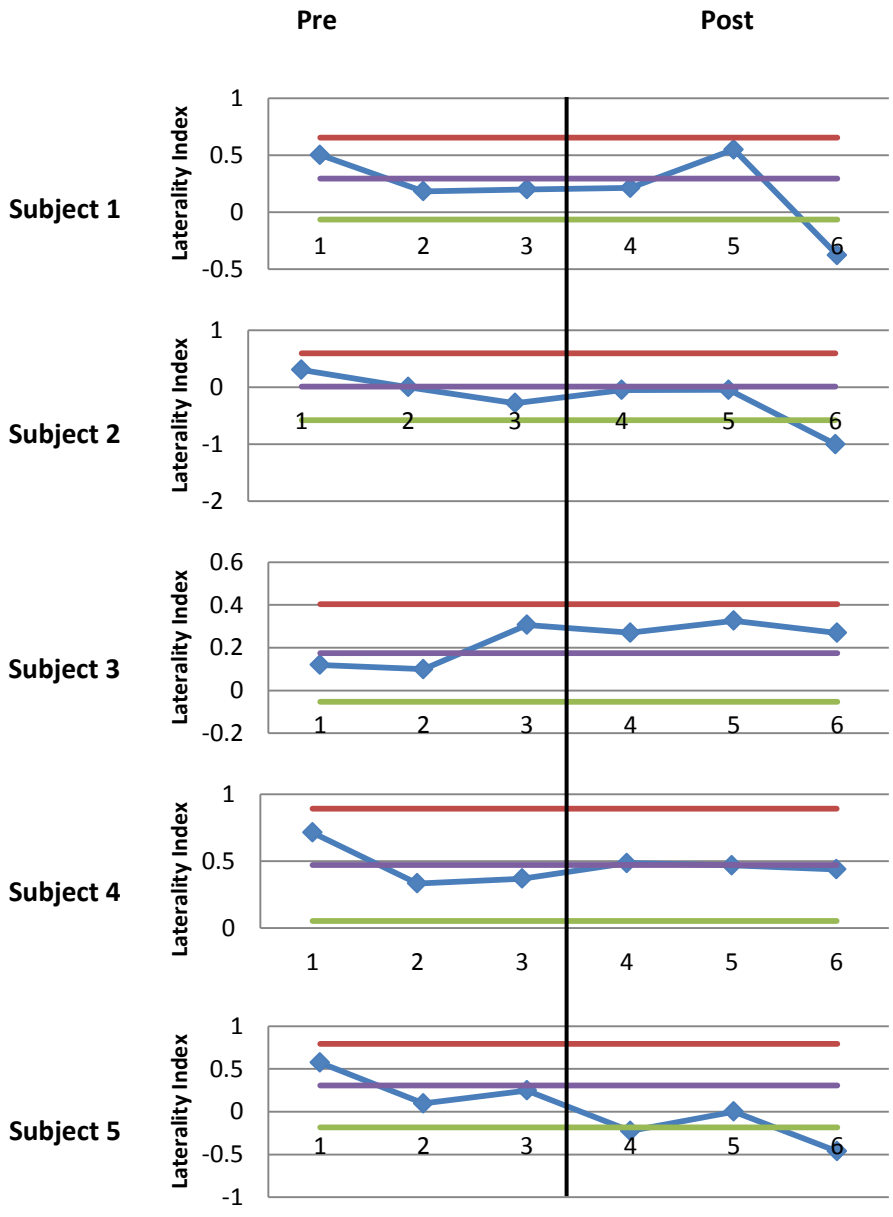


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

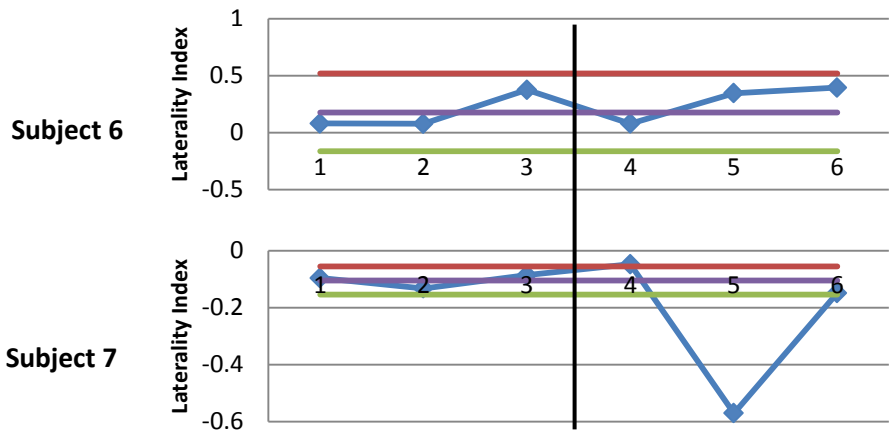


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 24: Precuneus Laterality Index (0+2 Back)

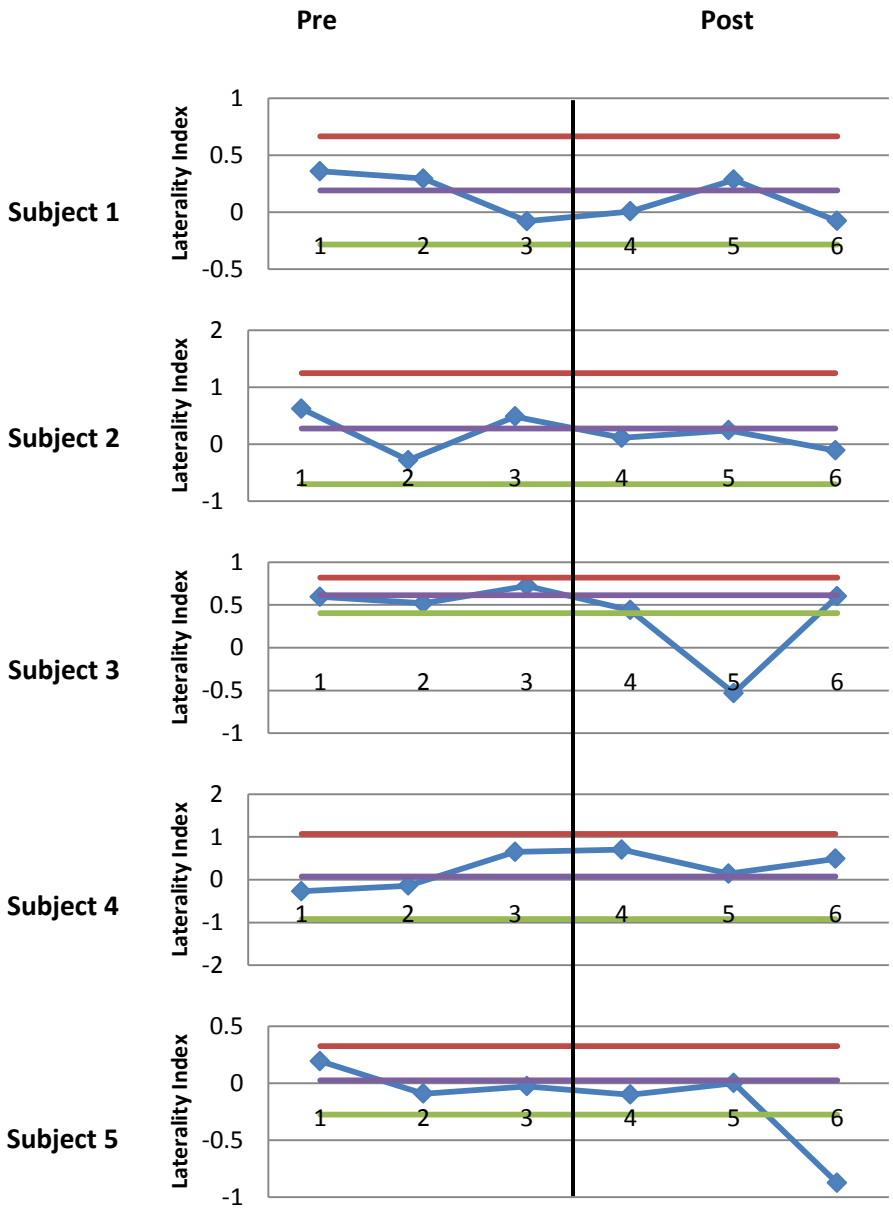


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

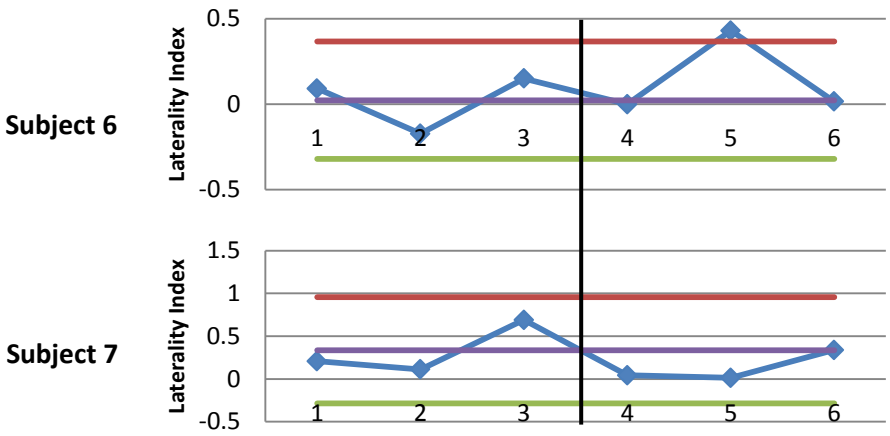


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 25: PCC Laterality Index (0 Back)

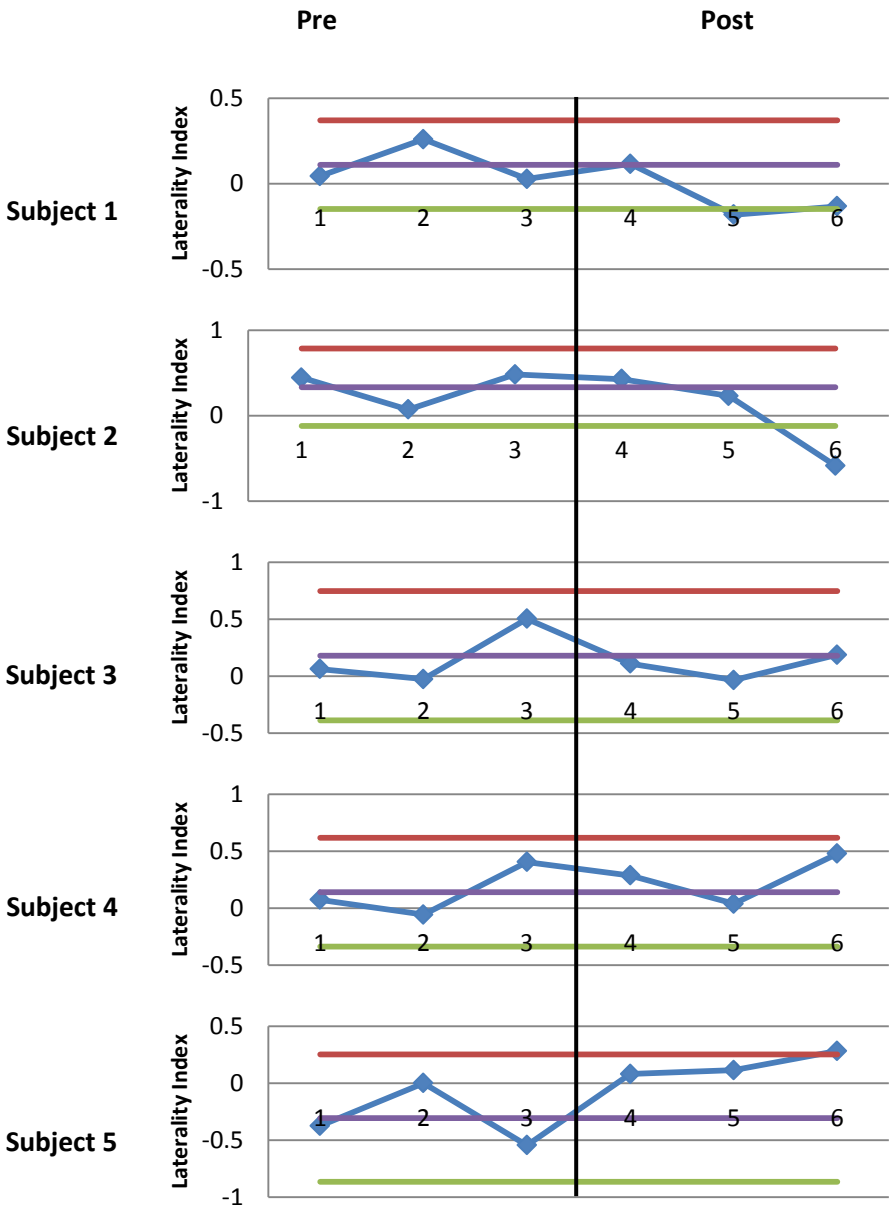


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

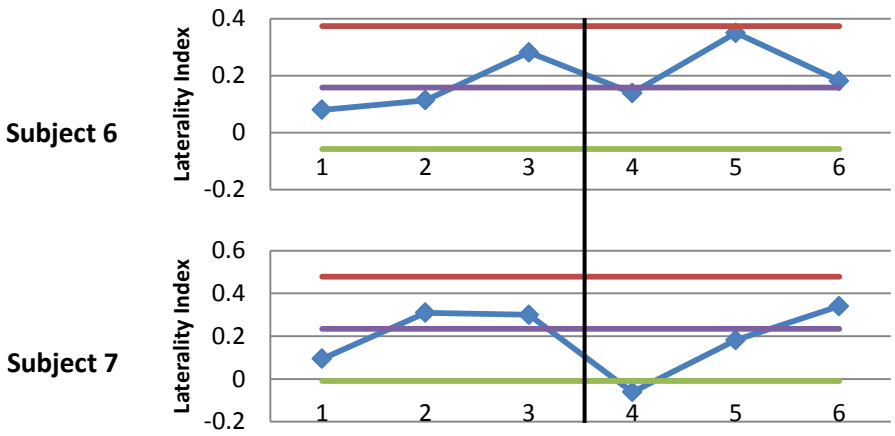


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 25: PCC Laterality Index (2 Back)

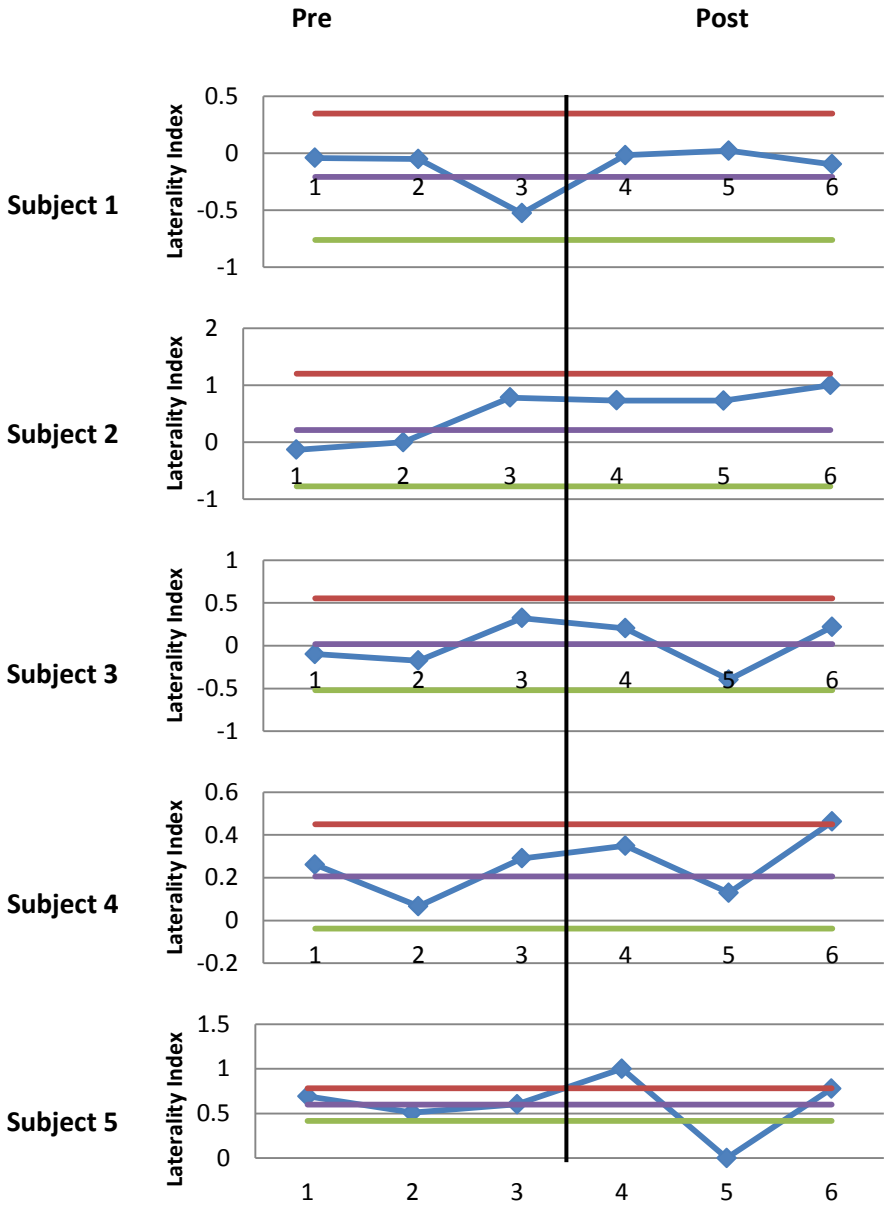


Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

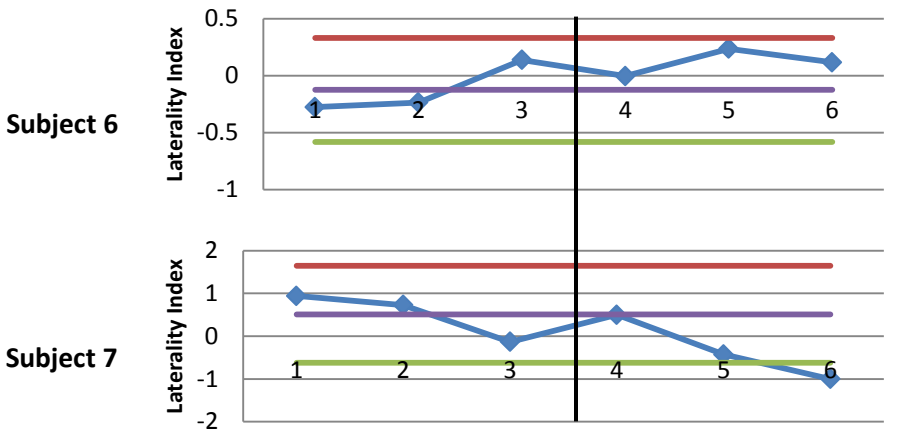


Upper bold line indicates 2 SD above mean; Center bold line indicates mea
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention

Appendix 25: PCC Laterality Index (0+2 Back)



Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention



Upper bold line indicates 2 SD above mean; Center bold line indicates mean
Lower bold line indicates 2 SD below mean; Vertical bold line indicates aerobic intervention