IDENTIFICATION OF THE NEUROBIOLOGICAL BASIS OF HEMODYNAMIC RESPONSES CORRELATED WITH COGNITIVE STROOP TASK PERFORMANCE AFTER AN ACUTE BOUT OF AEROBIC EXERCISE

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Cardiovascular activities may increase the brain blood flow improving neuronal activities leading to improved cognition. Consequently, the effects of an acute bout of moderate intensity aerobic exercise on brain hemodynamics and its correlation with cognitive color-word Stroop task performance were tested. The Stroop tasks were congruent (color matches word) and incongruent (color does not match word). Prefrontal (PFC) and motor cortex (MC) blood flow was recorded by fNIRS (functional near-infrared spectroscopy) while the subject was performing the Stroop tasks before and after the 30 minutes of exercise or equivalent time of rest controls (checking for practice effects). Ninety human subjects of age 24± 6, 20 ADHD (attention-deficit hyper-activity disorder), 27 High-BMI (>25), 29 males were recruited. Reaction time 'RT' decreased ($p<0.05$) after exercise for both the congruent (12%) and incongruent (10%) Stroop tasks, compared to 8% with practice alone. Accuracy did not change after practice or exercise. HR changes after exercise correlated ($p<0.05$) with better accuracy and faster RT for the incongruent Stroop task. In general, a metabolic lag occurred in the neuronal deoxy- hemoglobin (Hb) signals behind the systemic oxy-Hb signals. PFC showed the highest effect sizes of Stroop task-responsive systemic hemodynamic changes compared to baseline irrespective of rest or exercise. Yet, PFC showed most significant ($p<0.001$) neuronal hemodynamic changes between the before and after exercise sessions, and these changes were opposite for right and left PFC, and opposite for congruent and incongruent Stroop tasks. Correlating the RT and mistakes with hemodynamics for both the Stroop tasks revealed that, after

exercise, neuronal hemodynamic changes occurred at both PFC and MC associated with faster RT ($p<0.05$), and systemic hemodynamic responses occurred at PFC correlated ($p<0.05$) with mistakes. Overall, it was concluded that exercise changed the neuronal hemodynamic changes affecting speed; however, neuronal metabolic changes did not occur sufficiently to help improve accuracy in all subjects.

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I want to acknowledge my parents for encouraging me to go to graduate school and finish the dissertation writing process. I also dedicate my dissertation to my advisors and teachers over all these years that I have been in school.

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PFC	Prefrontal cortex
MC	Motor cortex
ADHD	Attention Deficit Hyperactivity Disorder
BMI	Body Mass Index
EF	Executive Function
RT	Reaction Time to respond to the Stroop Task
Hb	Hemoglobin Oxy-Hb (oxygen delivery, systemic) Deoxy-Hb (oxygen extraction, neuronal) Total-Hb (cerebral blood volume, systemic) Diff-Hb (cortical oxygenation, neuronal)
LSD	Least Square Differences (a *post hoc* analysis of the omnibus test).
Rho	Spearman's Ranked order correlation (Pearson's correlation on ranked order variables—non-parametric)

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction

In the cognition and exercise physiology literature, aerobic exercise of moderate intensity has been demonstrated to improve academic performance and cognitive functions (Schmidt et al., 2016; Hillman et al., 2009). The research on EF improvement after exercise is more rigorous for memory studies. Yet the studies on decision making, a type of EF, remain inconclusive. Some studies show improvement in both speed of decision making and accuracy after exercise, while some show improvement in only one parameter. Generally, however, more studies show that reaction time but not accuracy improves immediately after exercise (Frýbort et al., 2016; Rattray et al., 2013; Pearce et al., 2003). These 1differences most likely depend on the specific cognitive task studied and the specific pathophysiological state of the sample population. The present study has addressed the response conflict in naming the color and not the word in the incongruent Stroop task. The color-word Stroop task (Stroop, 1935) tests for selective attention to specific information during decision making and the inhibition of conflicting responses (interferences) when performing the Stroop task (MacLeod, 1991). An example of an incongruence in the Stroop task is showing the subject a colored word RED using blue print – in other words, the word and the color in which it is printed do not match. In this scenario, the subject reads the color and not the semantics of the word presented. Interference occurs when there is competition between conflicting choices of color and word. The Stroop effect is a highly reproducible effect and is associated with the longer response or reaction time taken in the incongruent stimulus compared to the congruent stimulus (MacLeod, 1991). These tasks were performed before and after exercise in individuals who were in one

or more of these populations:

- ADHD vs. non-ADHD
- Normal weight (≤25 kg/m^2) vs. High-BMI (>25 kg/m^2)
- Male vs female

The work of understanding the neural correlates of decision making needs to be further investigated. Contemporary researchers have shown that higher cerebral blood flow or higher oxygen delivery in the PFC of the brain immediately after exercise improves executive function. A reduction in reaction time occurs, but there is no change in accuracy (Lambrick et al., 2016; Byun et al., 2014; Giles et al., 2014; Ogoh et al., 2014; Tempest et al., 2014; Yanagisawa et al., 2010). Specifically, researchers report that an increase in global cerebral blood flow does not contribute to improved cognition. Neural activation changes, reflected by local cerebral blood flow changes at PFC, have contributed to improved reaction times immediately after exercise (Ogoh et al., 2014). To complicate matters further, high-intensity exercise interferes with the ability of local PFC circuitry to meet tissue metabolic demands, which in turn results in poor cognition in terms of decreased accuracy (Pearce et al, 2003). In fact, higher plasma norepinephrine and adrenocorticotropic hormone concentrations correlate with a decline in executive function after high intensity exercise (75% of maximal exercise intensity; Konishi et al., 2017). Maximal Exercise Intensity is the maximal intensity at which a human can possibly exert themselves during exercise. All the above evidence points to the alternative explanation that improvement of executive function by exercise (if it occurs at all) is through other mechanisms. These mechanisms could include the release of neurotransmitters rather than increased blood perfusion *per se* (Meeusen & Meirleir, 1995).

In humans, it is difficult to do invasive studies that have causal implications.

Instead, correlational studies using blood flow metrics has been used to estimate if changes in oxygenated blood perfusion immediately after exercise contributes to differences in behavioral performance in the Stroop task immediately after exercise. This study quantified the dynamics of oxy- and deoxy-hemoglobin changes in the brain (PFC and motor cortex) to interpret whether an acute bout of moderate intensity exercise improves blood flow *per se* which might enable increased neural activity and improved executive function. Addition of oxyhemoglobin (oxy-Hb) and deoxy-Hb components estimates the total cerebral blood volume, which in turn may predict the oxygen delivery to the brain. Deoxy-Hb reflects the oxygen extracted by the brain tissue, and so is an indirect measure of neural activation. If oxygen delivery (oxy-Hb + deoxy-Hb) is the primary hemodynamic variable affected and not deoxy-Hb, then it could be indicative of blood flow changes not affected by cerebral neural activation, but rather due to extraneous factors like neuro-hormone changes.

Executive function is challenged in individuals with ADHD (Attention Deficit Hyperactivity Disorder) (Nagashima et al., 2014; Sistino, 2013; Monden et al., 2012; Rosenberg & McCullough, 1981) or with a BMI (body Mass Index) over 25 kg/m^2 (Willeumier et al., 2011; Volkow et al., 2009). Moreover, it is unclear whether executive function changes effectively with an acute bout of exercise in the above populations. If the hemodynamic basis of improvement in cognition is oxygen delivery, then we would expect an improvement from an acute bout of exercise, which can change the effective oxygen concentration in the blood flow delivered to the brain. Sub-optimal regional blood perfusion, especially in the PFC, has been shown to be correlated with ADHD (Sistino, 2013). Thus immediately after exercise, even if there was an increase in blood flow, it may not have as much of an impact as in the non-ADHD population.

1.2 Physical Activity Effects on Academic Achievement

Academic achievement, measured with higher grade point average (GPA), was correlated with both acute and chronic aerobic exercise in the following studies. In nursing and kinesiology students in US colleges, higher aerobic activity (chronic) was associated with an increase in GPA) (χ^2 = 44.29, $p \leq 0.001$) (Bellar et al., 2014). However, these activities were reported after exercise had concluded and were chronic rather than acute exercise effects. The timing between aerobic exercises and the testing of academic achievement matter as well. There is an indication of better academic performance in the group performing aerobic exercises; however, these improvements in academic performances have not been tested right after the conclusion of the aerobic activity. Physical activity classes of moderate intensity improved academic performance on standardized tests by 6% (Donnelly et al., 2011). Acute bouts of treadmill walking at moderate intensity (60 percent of estimated maximum heart rate) for 20 minutes improved academic performance in reading comprehension by 5% (Hillman et al., 2009). In third and fourth graders, physical activity during recess time improved timing of on-task behavior during academic instruction by 20% (Mahar et al., 2006). Other kinds of exercises that include flexibility and muscle strength fitness caused no change in academic achievement (Castelli et al., 2007).Collectively, these data indicate that aerobic exercise improves academic performance, consistent with earlier conclusions by Hillman (2008).

1.3 Cognitive Functions and Cardiovascular Activities

Diamond (2015) reviewed the evidences of improvement in executive function with physical activity. –Per Diamond (2015) EF, a type of cognition related to goal-directed behavior includes:

- Inhibitory control (suppressing impulses)
- Selective attention (what do we pay attention to when we have multiple choices)
- Updating working memory (temporary memory storage to complete a task)
- Cognitive flexibility (switching between goals and tasks)

From these basic EFs arise higher-order EFs like planning, problem-solving, reasoning and decision making to choose the best alternative out of all available choices (Diamond,2015). From this review (Diamond, 2015) and its cross-reference article on resistance training by Liu-Ambrose (2010), we can fairly conclude that it was resistance training and not aerobic exercise that benefitted the Stroop effect. Submaximal acute effects of aerobic exercise for 60 minutes helped improve information-processing aspects of cognition per the meta-analysis conducted by Tomporowski (2003). Aerobic exercise acute effects made the RT go faster in the working memory task (however not the accuracy), and, subjects irrespective of their age had a positive arousal-affect. (Hogan et al. 2013).This indicated that aerobic exercise most likely made the RT faster and had positive physiological arousal (feel good) effects, which did not mean that cognition *per se* improved with aerobic exercise.

1.4 Oxygenated Blood Perfusion and Exercise Physiology

General systemic cardiovascular changes are likely to change tissue perfusion and oxygenation. If there is increased brain blood flow, the enhanced oxygen delivery could first affect structural connectivity, and then potentially affect the corresponding functional connectivity of the synapses between neurons at specific brain regions. These brain-related changes may affect decision making cognitive ability. In regular exercisers, increasing exercise intensity up to 84% of maximum heart rate for 30 minutes resulted in superior cognitive performance, which was attributed to improved

prefrontal cerebral oxygenation (Giles et al., 2014). The neural basis for exercise-associated improvement in EF is attributed to differential brain activation patterns, with increases in oxygenation within the PFC demonstrated by optical brain imaging (Tempest et al., 2014). However, there are conflicting studies that show that blood perfusion from the bilateral PFC decreases, along with associated declines in working memory and selective attention while subjects are simultaneously walking (moderate intensity aerobic activity) and performing cognitive tasks (McKendrick et al., 2017). These deficits in brain oxygenation were observed bilaterally at the PFC. Selective attention is a cognitive process where attention is paid to a particular stimulus when multiple stimuli are present. Decline in cognitive performance during exercise could be due to the competition for blood flow between physical activity and this selective attention.

The transient hypo-frontality hypothesis of Dietrich (2006) states that to compensate for the high neural activations in motor and supplemental motor areas of the brain facilitating exercise, other areas of the brain (e.g. prefrontal cortices) experience reduced oxygenation. Activities like the incongruent Stroop task that demand response selection tend to interfere with other activities such as exercise (more information on the Stroop tasks is presented in Chapter 2). This helps the experimenter create a situation where the finite metabolic resources may compete between the physical exercise and the incongruent task, much more than the competition of metabolic resources between exercise and congruent task. Ultimately, I predict that the subjects will achieve a lower score in the incongruent Stroop task than the congruent Stroop task right after an acute bout of exercise.

1.5 Neuroanatomical and Neurophysiological Correlates of Decision Making

The findings of Nogueira et al. (2017) depicts how the brain makes choices and how it integrates the values of a multitude of choices for each neuron that ultimately manifest as a final decision over time. In decision making tasks involving planning and response-inhibition, the ventromedial PFC (vmPFC) is correlated with affective decision making and the left dorsolateral (dlPFC) is correlated with response inhibition (Hutcherson et al., 2012). The right dorsolateral PFC (dlPFC) is associated with riskier decision making in healthy adults (Ye et al., 2015). Patients with right ventromedial PFC (medial orbitofrontal PFC) damage performed poorly in the Stroop color-word task, exhibiting the sensitivity of this test to lateral PFC deficits (Szatkowska et al., 2007). Impulsive decision making in violent patients correlates with lower neuronal density and reduced phosphate metabolism in the right medial PFC (ventromedial orbitofrontal cortex) when compared to healthy controls (Critchley et al., 2000). An overlap occurs in the brain circuitry of EF and Emotional Regulation (ER) in the PFC (Etkin et al., 2013). Emotional states affect the decision making, attention and working memory. Brodmann's areas 25, 12, 11 (right ventromedial-PFC) and 13 (insula) are associated with risky decision making involving reward and ER, self-regulation (decision making vs. ER), conflict resolution and behavioral control modulation (Clark et al., 2008; Hutcherson et al., 2012; Bechara et al., 2002; Critchley et al., 2000). Brodmann's areas 9, 10, 46 in the left dlPFC are involved with integrating multiple sources of information (Rivera et al., 2005; Hutcherson et al., 2012). Brodmann's areas 44, 45 in Broca's area or the Pars Triangularis (Left Ventrolateral PFC) are involved with semantic decision making, attention in speech processing, mirror neurons, reasoning, planning, working memory, ER (Hutcherson et al., 2012). Brodmann's areas 24, 31, 32, 33 (ACC) are involved in behavioral inhibition, motor

inhibition, impulse control, ER, attention, reading comprehension and working memory (Rivera et al., 2005; Ernst, 2003; Swick & Jovanovic, 2001; Maguire et al., 1999). Thus, PFC (Figure 1.1) was concluded to be involved in executive function (Hoshi et al., 2006).

Decision making neurons at the lateral intraparietal LIP cortex (within the PFC) are integrators of information from sensory neurons located in the medial temporal lobe for visually guided eye-movements (Lafer-Sousa & Conway, 2013) and connect to the corresponding motor neurons at the superior colliculus when decisions are made (Beck et al., 2008). For visual tasks the response chain takes the form of input sensory information processing at the middle temporal lobe sensory neurons, leading to decision making at lateral intraparietal cortex within the PFC (from where we measured) leading to motor bursts at the superior colliculus (Beck et al., 2008). Repetitive tasks often become reflexes and most activity shifts to the basal ganglia (which cannot be seen with fNIRS measurements).

Increased anterior cingulate cortex (ACC) (Figure 1.1) activity occured in the conflict-resolution decision making (Zaki et al., 2010). At the behavioral level, prolonged RT and increased mistakes in conflict-resolution tasks correlated with emotional decision making (Luo et al., 2014; Zaki et al., 2010; Ernst et al., 2003). Damage to the left mid-dorsal ACC resulted in lower accuracy in Stroop tests found in human lesion studies (Swick & Jovanovic, 2001). Miscommunication between the neocortex and the limbic system has been attributed to the malfunctioning ACC (Mériau et al., 2006). However, fNIRS was not capable of recording deeper layers like ACC, thus, in our study we focused on PFC and MC not on ACC.

Thus, in conclusion, prefrontal and motor cortices were areas of considerable interest for studying the decision making response in the brain.

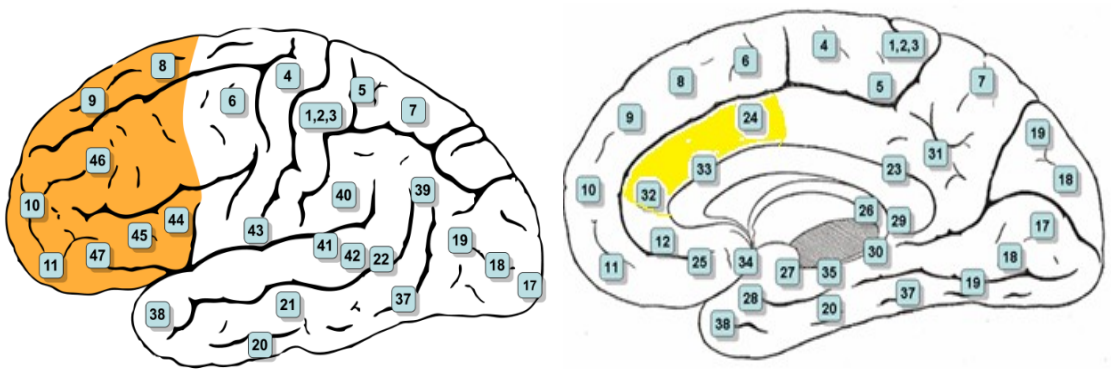


Figure 1.1. Brodmann's areas. Shaded areas are PFC (left) and ACC (right) (Brodmann 1918; Gray et al., 1918)

1.6 Theories of Neural Coding

Important to further investigation of the decision making are the specific theories of neural coding, which will be next explored. Tranquillo (2008) states in his book *Quantitative Neurophysiology* that neurons process information by encoding information and then communicating that information to other neurons in the brain. Thus, using spike train analysis (timing of action potentials obtained using EEG or electroencephalogram), the neural behavior at the cellular level can be decoded. Put differently, we can listen in to the neural messages (Tranquillo, 2008).

EEG estimates field potentials (electric potentials in the extracellular space around neurons), however, signals from specific brain location cannot be localized. fNIRS does a better job of spatial localization, however fNIRS does not estimate field potentials. Instead fNIRS estimate regional blood flow which could be correlated to field potentials via neurovascular coupling. The concept of neurovascular coupling has been discussed in Chapter 4. fNIRS can potentially identify increases and decreases on total action potential production in a certain brain region. More comparisons between the two techniques of EEG and fNIRS are in Chapter 7.

One of the assumptions of measurement of neural decoding of the brain signal obtained from EEGs is that the electrodes are placed at the same position and have

not been moved during the experiment. Yet this assumption can easily be violated. It is also assumed that all the neurons in the region being recorded from are firing at the same speed and are firing in the same direction. These assumptions can also easily be violated, because EEGs may represent neural activity from many different neurons firing in different directions. However, if there are multiple electrodes placed by triangulation, one can localize the EEG signal to a particular location. Also by signal-averaging across multiple trials (and by reducing signal-to-noise ratio), the signature of the neuronal firing is observed and thereby narrows down the rhythm. Since neuronal firing is proportional to the metabolic rate of the neurons (Tam & Zourdakis, 2014), it can be assumed that with the function Near-Infrared Spectroscopy (fNIRS) signal (which represent the metabolic rate of neurons), one can also decipher the neural code. By using fNIRS, the problem of localization of signal is better addressed than using the diffused signals of EEG.

In neural decoding, statistical tools like principal component analysis (PCA) are used to differentiate between two or more types of neuronal firing signals, such that one can 'bin' them into different groups in a process termed "spike sorting" (Tranquillo, 2008). A similar approach can be used for fNIRS studies to sort the signals.

1.6.1 Types of Neural Coding

1.6.1.1 Rate (Frequency) Coding

Neural information is encoded in the firing rate of a neuron (the number of spikes per unit time), which in turn is impacted by the synaptic inputs to the neuron. Even if the stimulus duration and amplitude remain the same but the stimulus is more frequently sent, then by the principle of temporal summation an action potential may fire (Tranquillo, 2008). Thus, the firing rate can determine the stimulus intensity and

predict how neurons encode information by rate (or frequency) coding. This firing rate is simply the scalar sum of the neuronal responses, and the higher this number the greater is the neuronal activity (Van Opstal, 2007). For example, the firing rate per rate coding in Figure 1.2 is 8 spikes/sec.

1.6.1.2 Temporal Coding

If the number of spikes per unit time (e.g. in 1 sec) remains the same but there is a temporal pattern with bursts of information distributed differentially over the same time duration, then this is termed temporal coding. In this type of neural encoding, the precise timing of neuronal firing is very important (Voegtlin, 2006). A higher stimulus may alter the precise timing of the action potential (Tranquillo, 2008). For example, the firing rate per rate coding in Figure 1.3 is still eight spikes/sec. but there is a temporal pattern or burst firing, which may signify a difference in how the neurons are encoding compared to the previous pattern. Temporal or rate coding could be applicable for a single neuron or for a group of neurons.

1.6.1.3 Place (or Labelled-Line) Coding

In rate coding, the neural firing in several neurons in one neuronal unit is averaged. However, in place coding the specific location of neural firing determines the overall neural firing pattern. To give an example, the perception of pitch in hearing depends on the site of stimulation in the basilar membrane in the cochlea (tonotopy), whose neurons project the perceptions to the brain in line (place coding) (von Bekesy, 1974). In place coding, neurons fire differently in different places and each neuron has a corresponding place where it fires the most. In labelled-line (or place coding), a specific neuron responds to a specific amount or scalar sum of neuronal firing (Van

Opstal, 2007). Evidence of labelled line (place) coding has also been observed in the PFC of rhesus monkey for a number-matching memory task (Neider & Martin, 2007) with an indication of rate coding followed by place coding (Van Opstal, 2007). Neider & Martin (2007) have studied tuning function, which reflects the peak function that maximizes when a set of neurons is tuned to the preferred numerosity (number naming cognition in brain). This corresponded to the tuning functions obtained for the numerosity in the intraparietal sulcus in humans (Piazza et al., 2004). That study was conducted using another brain blood flow measure called functional magnetic resonance imaging (fMRI) (see Chapter 5). In another fMRI study, Zimmermann et al. (2011) showed columnar like organization (labelled line coding) of direction-selective neurons (visual cortex) in the middle temporal area of humans. Figure 1.4 compares rate coding vs. place coding conceptually.

1.6.1.4 Population or Vector Coding

For each rate coding, temporal coding or place coding scheme, we may assume that firing is for a single neuronal unit comprised of nearby neurons that have the same preferred direction of firing. More realistically, however, there are multiple neurons that are being recorded simultaneously by the instrument and each have different preferred directions. A vector sum of them would lead to a single vector having a preferred direction and a summed amplitude of neuronal firing. This is what has been referred to as “population vector encoding” (Bear, 2007). The population vector coding has also been experimentally demonstrated by a decision making task (Beck et al. 2008). The probability distribution (associated with integration of evidence accumulation and selection of the decision optimally) is a Poisson like distribution of the population of spikes (Beck et al., 2008). At the mean value of this tuning curve,

the neurons respond most strongly to a stimulus. This is analogous to a count of the "votes" for all the neurons. The mean firing rate then corresponds to the neurons with the highest stimulation and with the preferred direction of firing. Population coding can be interpreted by neuroimaging techniques from the spatial-temporal neural response profiles (Panzeri et al., 2015). Cross-neuronal correlations of sparse (a few) cortical neurons is a metabolically efficient process and is very probable in the human brain. Pictorially population coding is depicted in Figure 1.5.

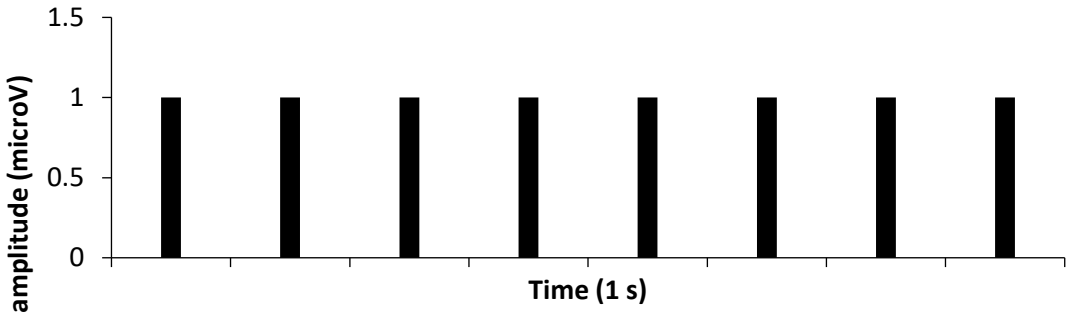


Figure 1.2. Rate coding. Rate coding can be used to estimate the number of spikes per unit time. The neuronal firing data (spikes) indicated could also be interpreted as hemodynamics data (correlated with neuronal firing) on the y-axis.

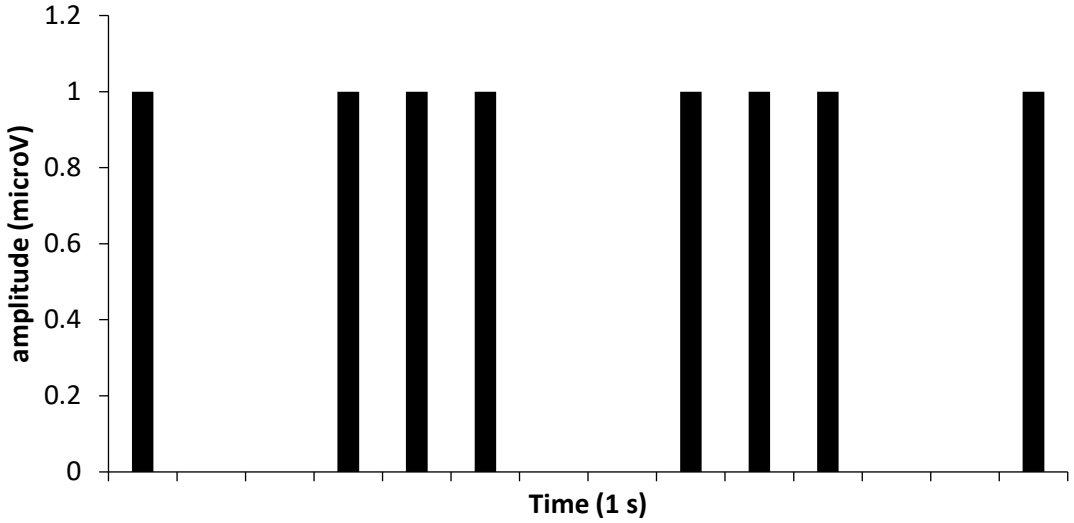


Figure 1.3. Temporal coding. This form of coding estimates the pattern of spikes generated temporally. The spike numbers per unit time may be the same as rate coding, as in Figure 1.2. However, the number of spikes are higher at a certain points in time compared to another within the same time-frame of 1 second. The neuronal firing data (spikes) indicated could also be interpreted as hemodynamics data (correlated with neuronal firing) on the y-axis.

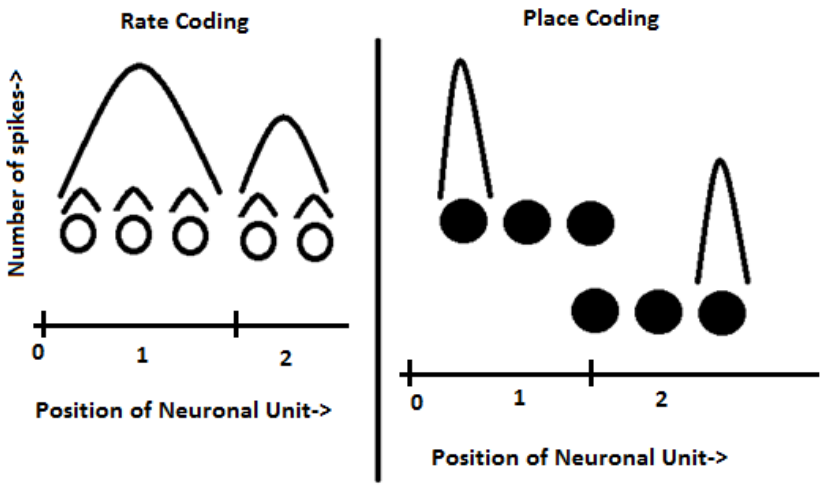


Figure 1.4. Rate vs. place coding. Rate coding describes the summation of signals from all neurons (open circles) in the neuronal unit (denoted by the horizontal axis). In place coding, the position of the neurons (closed circles) in the neuronal unit (denoted by the horizontal axis) decides the neuronal firing pattern and there is a correspondence between the exact neuron location with its function or the encoding pattern. The neuronal firing data (spikes) indicated could also be interpreted as hemodynamics data (correlated with neuronal firing) on the y-axis.

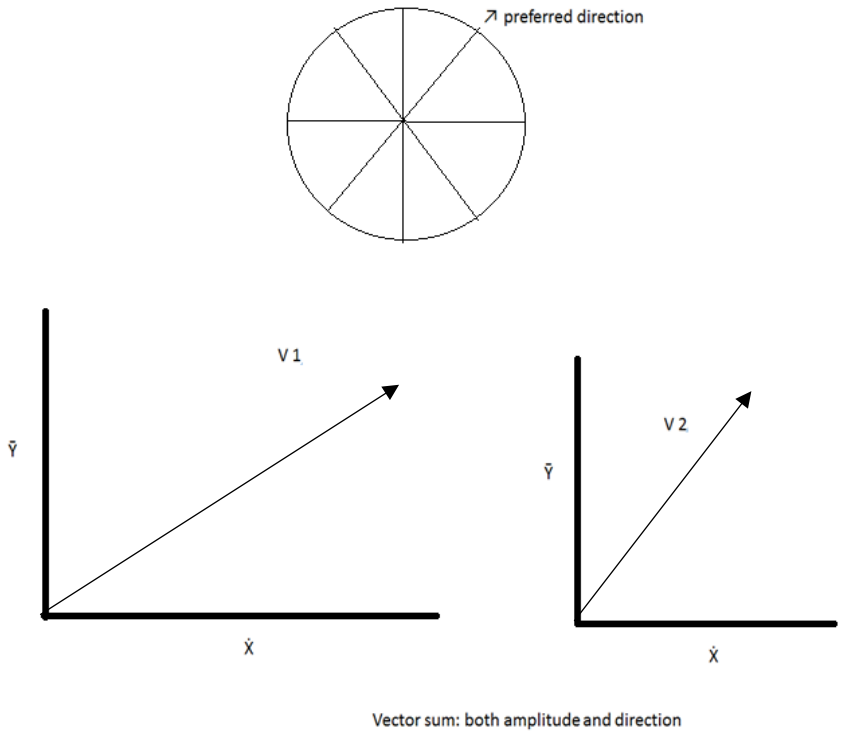


Figure 1.5. Population coding. The x-y plots (left) indicate the direction of neuronal firing of each of the two neurons in the neuronal unit. The circle (right) indicates the preferred direction of neural firing, which is determined by the vector sum of the directions of all neurons in the neuronal unit. The neuronal firing data (spikes) indicated could also be interpreted as hemodynamics data (correlated with neuronal firing) on the y-axis.

1.6.2 Choice of Neural Coding Schema in Current Analysis

The current study aims to correlate the neuronal response, determined by fNIRS signals, during the decision making task to the reaction times and accuracy of a test of cognition known as the Stroop test. Time-averaged hemodynamic signals were used for the analysis, which corresponded to rate coding for a sub-network of neurons close together in space. Thus, the choice of neural encoding schema being tested was population scalar rate coding, not population vector coding. The reason the present study chose rate coding over the other described types of neural coding schemas was due to the strong literature support of reaction time differences between incongruent and congruent Stroop tasks (Sahinoglu & Dogan, 2016; MacLeod, 1991; Stroop, 1935). Consequently, differences in the time-averaged hemodynamic signatures corresponding to the incongruent versus congruent tasks are expected, assuming rate coding of the neurons. Neurons in the brain (especially in the Lateral Intraparietal cortex of PFC) cooperate with each other and are involved in processing the information of color and word in parallel (Lafer-Sousa & Conway, 2013). Then the synaptic inputs merge together to discriminate the color from the word - i.e. the word is suppressed and then the color is identified (Miller 2013; Bogacz et al., 2006). I predicted that the prefrontal cortex has the ability to identify the color bias over the word. Channels could be better defined as the path between one emitter or source of light (light emitting diode in this study) including all its wavelengths and one photodetector. Overall, spatial (PFC and MC channels or brain locations) and scalar population rate (time-averaged hemodynamic signal) encoding are assumed while analyzing the fNIRS data. More advanced, spatio-temporal neural coding analysis (Ben-Eliezer & Frydman, 2011) is possible with the fNIRS data, however, for the purpose of this dissertation we shall use the approach outlined in Chapters 4 and 5.

1.7 Rationale for this Study

In this dissertation, blood oxygenation measures of the prefrontal and motor areas of the brain were correlated with decision making during Stroop tasks before and after an acute bout of aerobic exercise. I presumed that the reaction time improvements for both congruent and incongruent Stroop tasks after exercise would be a result of improved automaticity and quicker motor responses, evident from increased metabolic and cardiovascular changes in hemodynamic parameters (perfusion and oxygenation) after exercise selectively in the motor cortices and not in the PFC. This supposed improvement in the speed of cognition after exercise will likely be unrelated to response conflict monitoring implicated in the PFC, and will likely instead reflect motor effects of visual attention. After exercise, the total oxygenation in the PFC is expected to decrease to channel finite metabolic resources to motor cortices. Accuracy of the Stroop test, when measured objectively, is a better indication of cognitive performance after exercise. Indeed, in the literature we see ambiguity as to whether accuracy improves or not. I predicted that with high intensity exercises, cognitive performance will be reduced during and right after exercise because the mode of respiration shifted from aerobic to anaerobic. Improvements in cognitive performance after exercise that were specific to populations that usually had discrepancy in blood flow (e.g. high-BMI) can be expected after exercise and the associated increase in blood flow. In other words, metabolic changes associated immediately after exercise will not correlate with cognition benefits in the overall population, but rather will vary based on demographics of the test population. In addition, transient cardiovascular implications of acute exercise in cortical oxygenation may have no correlation to cognition at all.

1.8 Objectives

Against this backdrop, the objectives of this project were to:

- Quantify the brain-blood oxygenation responses from the prefrontal and motor cortices obtained by an optical brain imaging technique, and the heart rate responses obtained by a pulse oximeter, and identify whether the changes in hemodynamic responses were cardiovascular (systemic) or neuronal after exercise.
- Correlate these responses with the decision making parameters of reaction time/accuracy in the color-word Stroop task changes after an acute bout of 30 minutes of moderate intensity cardiovascular exercise. Identify whether the hemodynamic responses correlated with an improvement in the RT (faster speed) and fewer mistakes (better accuracy) after exercise correlate with cardiovascular (systemic) or neuronal hemodynamic responses.

Through achieving these goals, the following three specific hypotheses were tested, as will now be described.

1.9 Hypotheses

H1. Behavioral data.

H1A. After exercise compared to rest, RT for the Stroop tasks will be faster, however, accuracy will not change.

H2. Physiological cardiovascular responses.

H2A. After exercise, Heart Rate (HR) and Breathing Rate (BR) will increase.

H2B. HR changes during Stroop tasks will be correlated to improved cognitive performance in Stroop tasks (RT and/or accuracy) after exercise.

H3. Physiological brain hemodynamic responses. Hemodynamic responses would vary in intensity at different brain locations. After exercise, we hypothesize that the brain hemodynamic responses will change and that these changes will correlate with the behavioral performance (reaction time and accuracy) of the Stroop tasks.

H3A. In response to both the congruent and incongruent Stroop tasks, baseline-corrected hemodynamic responses mimicking neural activity will change

assuming rate scalar population coding. These task-responsive hemodynamic responses from the baseline (before exercise) would be both systemic and neural changes at the PFC and at the MC. Some or all the hemodynamic variables of oxy, deoxy, total and diff-Hb at PFC and MC will correlate with the RT and mistakes (behavioral data measures) for both congruent and incongruent Stroop tasks before exercise.

H3B. The systemic (but not neuronal) hemodynamic changes at PFC and MC following exercise will correspond to changes in the behavioral data. The MC hemodynamic changes after exercise will be higher than PFC changes during the Stroop tasks after exercise.

1.10 Specific Questions

Neural hemodynamic signals from PFC and MC in human subjects will be obtained using optical brain imaging technique (fNIRS) while the subjects performed the Stroop task eliciting decision making executive function, to determine which hemodynamic variable (oxy-, deoxy-, total-, diff-Hb) in the PFC (right or left) or MC had task-related changes from the pre-task baseline. More specifically, answers will be provided to the following questions.

- Changes in behavioral data after exercise?
- Changes in HR data after exercise and their correlation with behavioral data?
- Changes in hemodynamic response at PFC (prefrontal cortex) or MC (motor cortex) after exercise and their correlation with behavioral data?
- Are hemodynamic responses task-evoked? Are evoked responses neuronal or systemic?

Testing the hypotheses and sub-hypotheses given above will answer these key questions.

CHAPTER 2

COGNITIVE BEHAVIOR AND EXERCISE

2.1 Behavioral Measures of Cognition Impacted by Exercise

Considerable information is available about reaction times and decision making in humans from different demographics and under different physiological states. Reaction times in conflict-resolution decision making tasks improved by at least 10% after 30 min of cardiovascular exercise (Tam 2014). Irrespective of age and gender, aerobic exercise improved auditory and visual reaction times by 63% (Garg et al., 2013). Cardiovascular fitness improved the response accuracy of a working memory task by 6% in preadolescent children (Kamijo et al., 2011). Aerobically exercising adults had better formation of declarative memories by 5% in their first-trial learning tasks (Pereira et al., 2007). Adolescent groups that had carried coordinative exercises did better by 43% in terms of response accuracy in attention and concentration tasks, when compared to 10% improvement in response accuracy after a normal sports lesson exercise (Budde et al., 2008).

Collectively, these data show that aerobic exercise improves reaction times in decision making tasks, and other aspects of executive function like working memory, concentration as well.

2.2 Optimum Range of Aerobic Exercise that Facilitates Cognition

Reaction times in decision making tasks gradually decrease during progressively higher (but less than the maximal intensity) bouts of aerobic exercise (cycling). Such bouts improve the speed of decision making by 8.3% with sub-maximal or moderate intensity in trained healthy men (Ogoh et al., 2014). However, in that study the accuracy of performance remained unchanged in trained healthy men.

Moreover, physical stress in the form of higher heart rate (above 80% of the maximum) after exercise lead to higher errors and thus poorer decision making (Pearce et al., 2003). Studies confirmed that moderate intensity aerobic exercise improved response-inhibition involving cognitive task speed by 22%, but accuracy was not affected (Rattray et al., 2013). In soccer players, increased aerobic exercise intensity did not affect accuracy of visual-attention decision making tasks, but did improve by 2.29% the motor response time or the speed of reaction times (Frýbort et al., 2016). Increased submaximal aerobic exercise intensities led to exercise induced physiological arousal (sweating, higher heartbeat, etc.) in soccer players (experienced or inexperienced), which led to a 14% improvement in the speed of decision making but no change in accuracy (Fontana et al., 2009). In another set of studies, decision making accuracy for the goal-directed behavior of passing the ball improved by 33% in soccer players, although dribbling and shooting did not improve after training in a dynamic visual scene cognitive- training task (Romeas et al., 2016). Professional road cyclists (as opposed to recreational road cyclists) performed better by 20% (as opposed to 10% in recreational road cyclists) in the reaction time of inhibitory control decision making task. Professional road cyclists had 22% more correct responses than recreational road cyclists during the inhibitory control decision making task (Martin et al., 2016).

Overall, then moderate but not high intensity exercise appears to facilitate cognitive speed, but does not improve accuracy of decision making.

2.3 How do Exercise and Disease State Influence Decision Making?

In the literature, there is evidence that pathological states like ADHD or high-BMI contributes to differences in decision making. Children with lower inhibitory control benefitted most from single bouts of moderate-intensity exercise compared to children

with normal inhibitory control (Drollette et al., 2014). Children with lower inhibitory control had better response accuracy by 18% in resolving conflict and also had better reaction times (by 3%) in the cognitive task. However, the control population only improved the reaction times by 1%, with no change in accuracy (Drollette et al., 2014). Response accuracy for inhibition control in preadolescent children improved significantly by 7% immediately after exercise, but the reaction times remained unaffected with acute bouts of exercise (Hillman et al., 2009).

The difference in improvement in accuracy or reaction times in decision making tasks in some studies, but not in others, may be due to differences in paradigms for testing cognition. However, differences may also arise from differences in the physiological states of the populations. Thus, there seems to be a discrepancy in the research in terms of improvement of speed and accuracy of decision making immediately after exercise. Some studies find improvement in both speed and accuracy while others find improvement in speed but not accuracy. Still others find improvement in accuracy but not speed. It appears that exercise allows for better brain blood flow, in people having difficulty in inhibition-control (like in ADHD), which in turn leads to self-correction and fewer errors. In doing so, however, performance speed is compromised. For normal healthy controls exercise did not impact accuracy as blood flow was already optimum, but an acute bout of exercise made the normal, healthy subjects faster as a result of the sympathetic reflexes.

2.4 Conflict-Resolution Aspect of Decision Making as Measured by Stroop Tasks

Stroop-like interference can also be demonstrated using a big and small circle, where the subject had to say “big” when seeing the small circle, and *vice versa* (Ikeda et al., 2014). In Ikeda et al.’s (2014) study, Stroop tasks involved low working memory,

and so this study did not test the working memory aspect of EF. Instead, the incongruent Stroop task probes the inhibition control aspect of EF.

Different models have been developed to explain the Stroop interference. According to the bottleneck model of attention (Kahneman, 1973), there is a frequent suppression or queuing in the organization of motor responses where only one stimulus or one response is operational concurrently. When two stimuli are simultaneously presented, the easier one is perceived immediately and the sensory information of the other creates no response until after the perceptual analysis of the first message is complete. In this model, attention controlled perception and the bottleneck is located at or just before the response selection.

According to the capacity model of attention (Kahneman, 1973), there is a performance limit to performing these cognitive tasks that can be enhanced by exercise-induced stressors. This decision bottleneck or competition for effort in a dual task paradigm can be tested by the Stroop task, where the two competitive stimuli of color and word limit the overall cognitive performance in the incongruent Stroop task.

2.5 Theories of Decision Making Brain Circuitry

In the Stroop task, the neurons in the brain bias information processing to extract the color and not the word. A group of neurons should have a way of encoding and decoding the features of the word and color during the Stroop color-word identification task. One hypothesis is that the brain circuitry is versatile and the same circuitry at one point in time identifies “color” and at another point identifies “word”. That is, the encoding process for the word-color are equal. The alternate hypothesis is that, since the brain processes word faster (as noted above) than color, the brain must inhibit or suppress the word to successfully identify the color. Several models

have been proposed to account for these hypotheses.

2.5.1 Horse Race Model

In the horse race model for the Stroop effect, the word is processed faster than the color because word naming is considered an automatic (involuntary) response (Morton & Chambers, 1973). Dunbar & Macleod (1984) pointed out the insufficiency of the horse race model to explain the Stroop effect, suggesting an alternative interactive model where interference occurred because of priming the wrong responses. This modified model is a feedforward mechanism of cognitive processing that resulted in the ultimate response of choosing the color and not the word in the Stroop task. In the above race model, a two-dimensional model of decision making (color and word) has two separate integrators or two alternative choices — both are processed independently and in parallel. In the first choice (in this case the word) wins the "race" over the color (Miller 2013; Bogacz et al., 2006).

2.5.2 Drift Diffusion Model (DDM).

In this one-dimensional model (for two-alternative forced choice decision making) for the Stroop tasks, the encoding of the color and word were unequal. The differences between the input sensations for the two choices and the inhibitions between the alternative decisions accumulated to integrate into the final decision. In this model, the alternative integrator was suppressed or inhibited. Eventually there was an accumulation of the final integration of neural activities crossing the threshold (Nogueira et al., 2017; Miller 2013; Bogacz et al., 2010; Lafer-Sousa & Conway, 2013).

The DDM is the preferred model for interpreting the brain circuitry during decision making task (Bogacz et al., 2010). This became apparent when speed-

accuracy tradeoff in the decision making task was manipulated depending on which parameter (speed or accuracy) was being rewarded. The results indicated that there is some sort of integration of individual responses that accumulate over time to generate a final decision supporting the DDM model (Bogacz et al., 2010).

2.5.3 Speed-Accuracy Tradeoff Modelling

In addition to decision making modelling, there are also sequential sampling models of speed-accuracy tradeoff (faster speed compromises accuracy) in decision making tasks. In such models, the speed-accuracy tradeoff depends on the accumulation of sensory information from a population of neurons over time, where the brain makes a statistical probability distribution to determine the final decision (Lafer-Sousa & Conway, 2013).

2.5.4 Cohen Model

The Cohen model consists of parallel distributed processing of attention to the color and word inputs in a Stroop task. This model is a widely accepted model for the typical reaction time response seen in the incongruent versus congruent tasks (Cohen, 1990; Stafford & Gurney, 2007). This model depicts the feedforward two-tier network inputs of color and word to finally reach the response selection of an output based on evidence accumulation. Neuroanatomical parallels of the Cohen model (Cohen et al., 1990) have been drawn to the neuroanatomical connections between the cortex, basal ganglia and thalamic complex, with the basal ganglia being implicated for the response (output) selection (Stafford & Gurney, 2007).

The inhibition-based Cohen model and DDM model may be even more applicable for decision making in people who have inefficient inhibition control (like

ADHD). For this reason, the present study used the decision making Stroop task on all populations and ADHD status was noted during the data analysis.

2.5.5 Neural Encoding for the Stroop Tasks

The brain may use a mean firing rate of a group of neurons with similar functions for the decision-making task, or the brain may use a linear combination of firing rates of many different neurons and their interactions or projections to one another (output) for making the final decision (Beck et al, 2008). Hypothesis (*H3A*) states that the brain uses interactions between different neurons for the decision making task instead of acting in isolation (scalar population coding). The reaction times then vary because of the differential neural encoding, and these changes are reflected in the hemodynamic responses. It is also hypothesized that the brain could be using votes of several neurons with the majority winning (rate coding along with scalar population coding). (See section 1.6, above, for neural encoding schema).

2.6 Materials and Methods

2.6.1 Participants in the Study

The Institutional Review Board (IRB) guidelines of University of North Texas UNT Denton, (IRB #14453) were followed in the recruitment of the subjects. Adults signed an informed consent form and, for minors, their guardian signed a consent form. Table 2.1 depicts the demographics of the test population.

Figure 2.1 depicts the overall research design (block design) where alternative blocks of congruent and incongruent Stroop tasks were administered. During the Stroop tasks optical brain imaging using fNIRS were additionally recorded from prefrontal and motor cortices in the studies described in Chapters 4 and 5.

Table 2.1. Demographics of participants, Mean ± S.E.

Experiment	n	Age	Gender	ADHD	BMI
Exercise	73	23± 5	22 Males 51 Females	17	High (>25 kg/m^2)-BMI: 21; Normal-BMI (≤25 kg/m^2): 52
Non exercise	30	23± 5	11 Males 18 Females	6	High (>25 kg/m^2)-BMI: 13; Normal-BMI(≤25 kg/m^2): 16
Overlap	13	24± 6	4 Males 9 Females	3	High (>25 kg/m^2)-BMI: 7; Normal-BMI(≤25 kg/m^2): 6

2.6.2 Stroop Tasks

The human subjects in this study performed both the congruent and incongruent Stroop tasks. The congruent Stroop task is a color-identification test for a color-word that is printed in the same color as the word (e.g., the word “RED” is printed in red color) (see Figure 2.2). The incongruent Stroop task is a color-identification test for a color-word combination where the word and the color in which it is printed differ (e.g. the word “RED” is printed in blue color) (see Figure 2.3). The conflict-resolution decision making involved in this Stroop color-word test task identified the color and not the word.

The subjects performed the congruent and incongruent color-word Stroop task alternatively for 10 trials each (mixed-block-design). The subjects were asked to read out loud the color of 40 randomized printed words on a computer screen (see Figures 2.2 and 2.3) as rapidly as possible in each trial. Therefore, the priming was for response speed and not for response accuracy. A computer presenting the screens with the word for the trials recorded the timing for the completion of the above task, and the experimenter recorded the accuracy of the color-identification. There were 10 alternating blocks of congruent and incongruent Stroop tasks. Each block consisted of 40 words, as depicted in Figure 2.2 and Figure 2.3. In addition, the design was pseudo-randomized such that two sets of each of the congruent and the incongruent Stroop tasks were alternated (http://biology.unt.edu/~tam/Science/StroopTest.html).

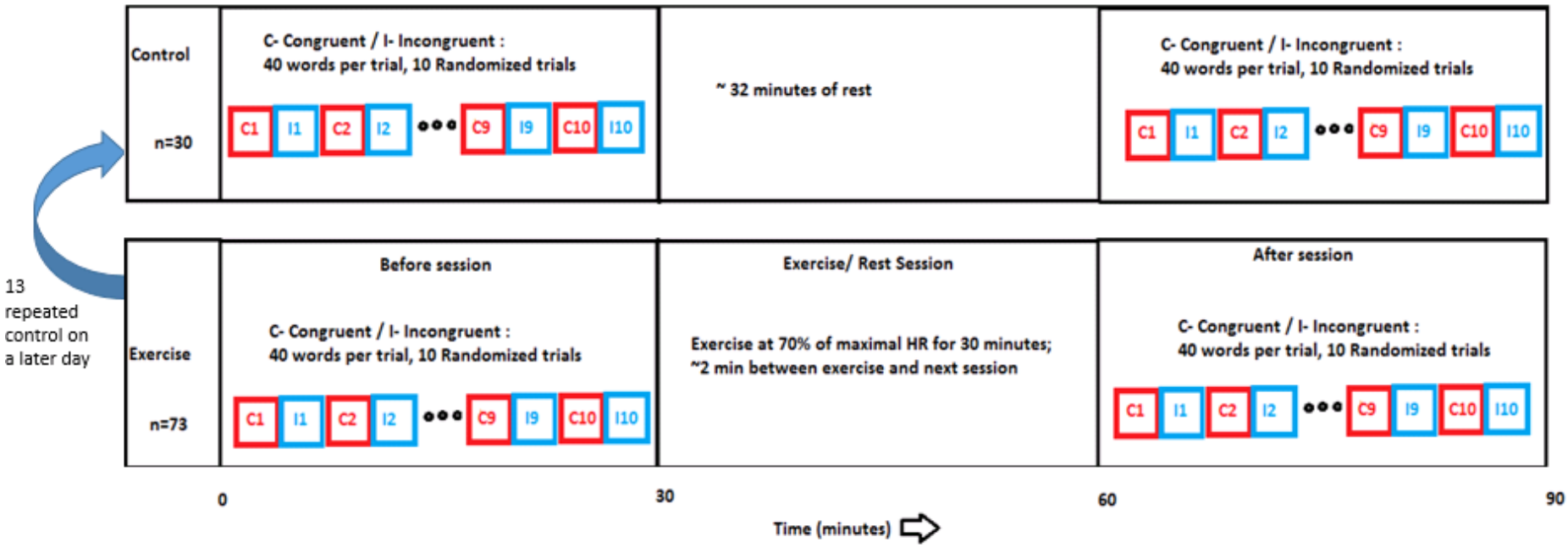


Figure 2.1. Overall research design. Each trial block represented by rectangles (red were the congruent trials), blue were incongruent trials. There were total of 10 congruent trials alternated by 10 incongruent trials that were randomized in each session. Each trial consisted of 40 words. Each congruent trial took about 12 secs, and each incongruent trial took about 40 secs. There were total of 103 runs, out of which 73 runs were for the exercise experiment and 30 for the control experiment. 13 people from the exercise experiment came back on a different day for the control experiment.

Figure 2.2. Congruent Stroop task (color matches the word).

Figure 2.3. Incongruent Stroop color-word task (reading the color and not the word).

2.6.3 Rest (Control)

As a control for the practice that would likely result from the Stroop tasks being conducted multiple times, subjects participated in separate, rest (control) trials in which they recorded the Stroop tasks before and after 30 minutes of rest or sedentary

activity. If the same subjects who did the exercise experiments volunteered to be a part of this rest (control) experiments, they returned on a later day and did the same experiment, except that instead of exercising for 30 minutes they did the sedentary activities.

2.6.4 Exercise

Subjects performed the cognitive Stroop tasks before and after 30 minutes of an aerobic exercise at moderate intensity (70% of maximal HR). 70% of the maximal heart rate was determined by their age. According to the National Heart, Lung and Blood Institute, subtracting the person's age from 220 estimates that person's maximal heart rate (Mikus et al., 2009). Thus, for a person of age 20, their maximal heart rate was determined to be 200 bpm. Thus, 70% of the maximal heart rate for this person was 140 bpm. Aerobic exercise was performed on a stationary bike (Cardio Dual Trainer, BRM 3671/3681/3690) that could be alternatively used as an elliptical. Table 2.1 depicts the outline of the behavioral data collected.

Table 2.2. Outline of behavioral data collected.

Experiments	Treatments	Behavioral Data
I Congruent II. Incongruent	Exercise (n=73) Control (n=30)	1. Reaction Time (RT) 2. Error

2.7 Data Analysis Techniques

2.7.1 Speed-Accuracy Tradeoff Modelling

The speed or reaction time (RT) was plotted against accuracy (number of mistakes, that is the number of errors in the Stroop tasks) to determine if there was a speed-accuracy tradeoff in each of the experiments of before rest (control) and after

rest (control) and before exercise (experiment) and after exercise (experiment) for the congruent and incongruent Stroop tasks. Also this test helped us determine if both the estimators of RT and mistakes were accounting for the subject paying attention to the Stroop tasks.

2.7.2 Bar Graphs for Change in RT and Mistakes with Rest and Exercise

We wanted to determine if the % changes in behavioral data were due to repeated measurements but indeed were an impact of exercise. Thus, the % changes in RT and mistakes immediately after exercise experiments were compared against the changes immediately after rest controls. Bar graphs were plotted with the mean and standard errors (S.E.) of the change % in the RT and mistakes for the congruent and incongruent Stroop tasks in the rest control and exercise experiment.

Mean % change in RT was calculated as the difference in average RT in all the 10 trials after - before exercise, divided by before exercise, times 100. This was a normalized measure for all the participants.

Since there were 40 words in each trial, the mistake rate percentage in each trial was calculated as [number of mistakes per trial X 100]/40. This allowed for the standardization of the mistakes rate in all subjects, after the methodology of Lucas et al. (2012). Then the mistake rate percentage was averaged for the 10 trials before and after exercise and difference of after – before was the percentage change in mistake rate.

2.7.3 Distribution of % Changes in RT and Mistakes After-Before Exercise.

Histograms and box plots were created for the change in the RT and mistakes data to determine if the changes in the distribution was positive or negative and

whether the data was normally distributed or not. A Shapiro-Wilk test of normality was also conducted to confirm whether the distributions were normal.

2.7.4 Non-Parametric t-Tests

The objective of this test was to compare the before and after sessions, meaning the session before or after was the independent variable. The dependent variables were the changes in RT and changes in accuracy. Since these changes were in the same subjects and were repeated measures, and because the paired differences between the before and after sessions were not normally distributed, the non-parametric version of a paired t-tests called Wilcoxon-signed-rank-t-test was employed, using SPSS software. The non-parametric version of Repeated Measures ANOVA (RM-ANOVA) general linear model called Freidman Rank Sum test for the before and after sessions could also have been chosen. However, the same *p*-value emerged for both the Wilcoxon signed rank and Freidman tests. For the exercise group, there were 73 participants, and for the control rest group there were 30 participants. The non-parametric Wilcoxon-signed-rank test was used to compare before and after control, or before and after exercise.

2.7.5 Independent Samples t-Tests to Compare Exercise from Practice Effect

The dependent variables were % changes in RT and mistakes rate, and they were analyzed separately in two different Mann-Whitney U tests (non-parametric t-tests to compare % changes after exercise from % changes after rest controls). In addition, congruent Stroop tasks were analyzed separately from incongruent Stroop tasks. These tests were performed on the pooled exercise and control data, and this

could help us determine the exercise effects from the practice effects of repeating the Stroop tasks multiple times.

2.8 Results

2.8.1 Speed-Accuracy Tradeoff

The incongruent Stroop tasks showed a significant (p<0.05) RT- mistakes correlation (Figure 2.4), but only for the novel conditions before exercise and before rest. This correlation between the RT and number of mistakes variables disappeared following both exercise and rest conditions. There was no RT-mistakes correlation seen for the congruent Stroop tasks. The subjects making more mistakes were also slower and vice versa; attentional problems would compromise the performance of the incongruent Stroop effect. There was an outlier in the exercise data, who was not paying much attention to the cognitive incongruent Stroop task and was making more mistakes but was that person was very fast or had a faster RT (this case was an example of speed-accuracy tradeoff which was generally not seen in most of the population). Since both RT and number of mistakes were indicators of attention to the Stroop tasks, both were analyzed in the subsequent analyses.

2.8.2 Change in RT Immediately After Rest and Exercise

The % change in RT for both the congruent and incongruent Stroop tasks were significantly faster (p <0.001, n =73) by about 10% after exercise (Figure 2.5) as determined by the Wilcoxon signed rank tests. In addition, percentage changes in RT for both the congruent and incongruent Stroop tasks were significantly faster (p <0.001, n=30) by about 8% after practice (rest) (Figure 2.5). Immediately after exercise (n=73) or without exercise (n=30), no significant changes were observed in the number

of errors in the congruent and incongruent Stroop tasks. The changes have been represented by bar graphs of the mean and standard error in Figure 2.5. There were exercise specific effects where both the congruent and incongruent Stroop tasks after exercise differed significantly from the after rest (controls) by $p<0.06$ as determined by the Mann-Whitney U tests.

2.8.3 Change in Accuracy Immediately After Rest and Exercise

Similarly, we determined if there was a % change in accuracy immediately after the control rest condition and immediately after exercise, however, there were no significant changes. The % changes in mistakes rate have been represented by bar graphs of the mean and standard error in Figure 2.6. There were exercise specific effects where both the congruent and incongruent Stroop tasks after exercise did not differ significantly from the after rest (controls) by $p=0.63$ for congruent and $p=0.34$ for incongruent Stroop as determined by the Mann-Whitney U tests.

2.8.4 Distributions of RT Changes Immediately After Exercise

The distributions of the change in RT after exercise for the congruent and incongruent Stroop tasks (n=73) were depicted by histograms and by boxplots in Figure 2.7. Generally, RT decreased or speed became faster after exercise. The percentage change in RT immediately after exercise was normally distributed for the incongruent Stroop tasks and but not normally distributed for the congruent Stroop tasks as demonstrated in Figure 2.7 and Table 2.3.

2.8.5 Distributions of Mistakes Changes Immediately After Exercise

The change in accuracy rates after exercise for the congruent and incongruent

Stroop tasks (n=73) is depicted by histograms and boxplots in Figure 2.8. Comparing the mistakes rates post-exercise for the congruent and incongruent tasks indicated that there was no net change in mistakes, as reflected by the median zero for both congruent and incongruent trials in Table 2.4 and Figure 2.8. Yet, the variance was higher for the incongruent trials. Moreover, the positive skew in the distribution of mistakes rate Figure 2.8 B, specifically for the incongruent Stroop task, meant that more subjects made fewer mistakes during exercise (although some subjects did make more mistakes after exercise).

2.8.6 Use and Outcome of Non-Parametric Statistics

The relative percentage change (standardized measures) in the congruent RT was not normally distributed (the distribution was not Gaussian) where the corresponding mean and median were not equal (Table 2.3). The absolute non-standardized changes in the RT data for both the congruent and incongruent tasks were not normally distributed. In addition, the RT distributions in some individual subjects were not normal, so non-parametric statistics were used when applicable. For such distributions, use of median rather than mean may be a better representation of central tendency. In addition, parametric tests were not appropriate for non-normally distributed data. In contrast, the relative percentage changes in incongruent RT distribution was normally distributed, with equal means and medians (Table 2.3 and Figure 2.7).

Changes in test accuracy were presented in Table 2.4 and Figure 2.8. Since the changes in the number of errors could sometimes be zero, use of standardized non-parametric test statistic of Spearman's Ranked correlation was also beneficial for correlating behavioral data with demographic or physiological data.

Non-parametric Wilcoxon signed rank t-tests were used to compare before and after sessions, and non-parametric Mann-Whitney U tests were used to compare independent samples of exercise from rest controls.

RT differed significantly at $p<0.001$ as noted in 2.8.2 between the before and after sessions both for control rest and experiment exercise for both congruent and incongruent Stroop tasks. In addition, there were significant differences between the exercise and rest controls at $p<0.06$ both for congruent and incongruent RT, also noted in section 2.8.2. Furthermore, there were no significant differences in mistakes between before and after sessions for neither the rest nor exercise, nor between the exercise and rest control groups as noted in section 2.8.3.

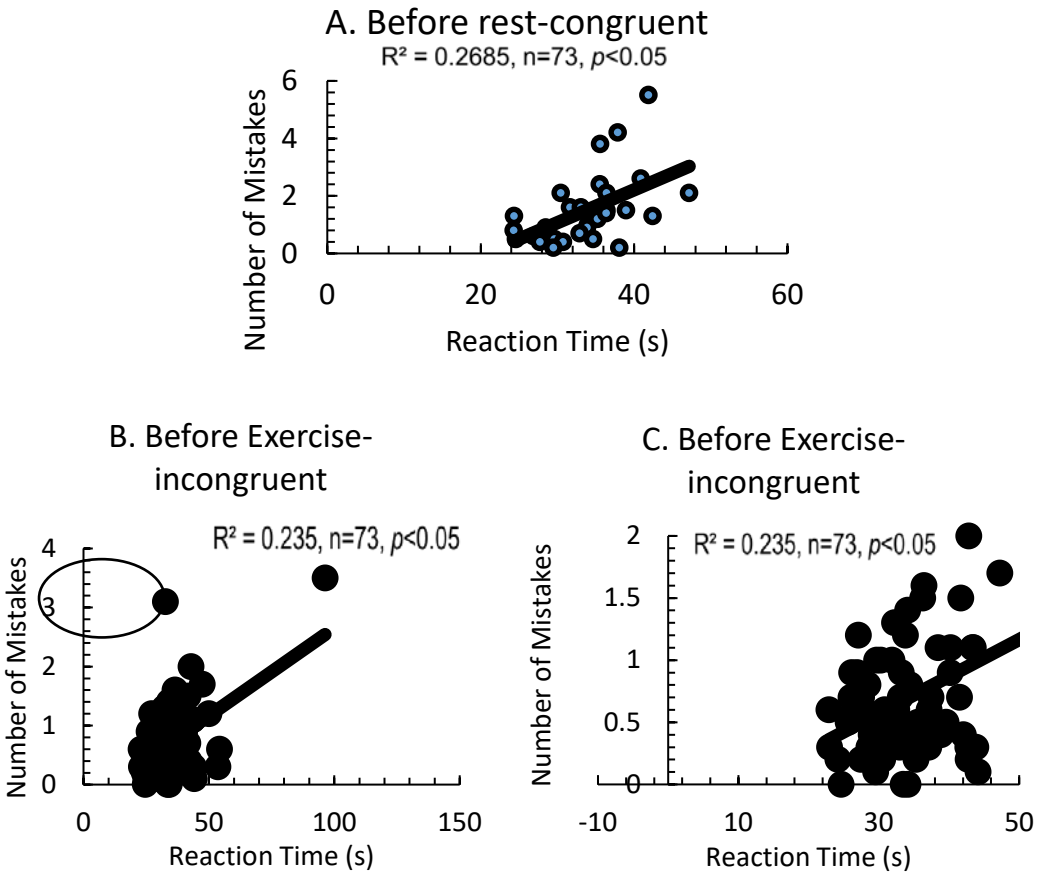


Figure 2.4. RT- Number of mistakes correlation. Speed-accuracy tradeoff seen in the outlier marked. For both the incongruent tasks before rest experiment (A), n=30, p<0.05, Pearson R= 0.52 and before exercise experiment (B, with outlier) and (C, without outlier), n=73, $p<0.05$, Pearson R= 0.48, we see significant positive correlation meaning greater the number of mistakes slower the participant.

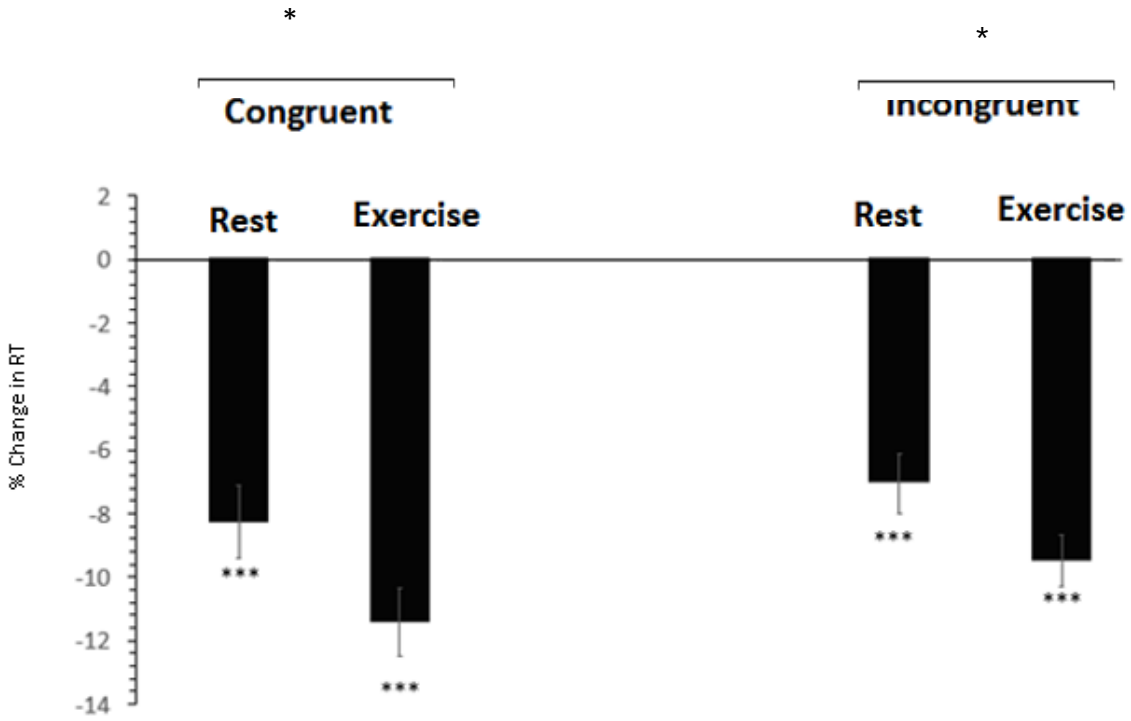


Figure 2.5. Change in RT immediately after rest and exercise (represented by bar graphs of Means and S.E.). *** $p<0.001$ Wilcoxon-signed rank t-test. * $p<0.06$ Mann-Whitney U tests.

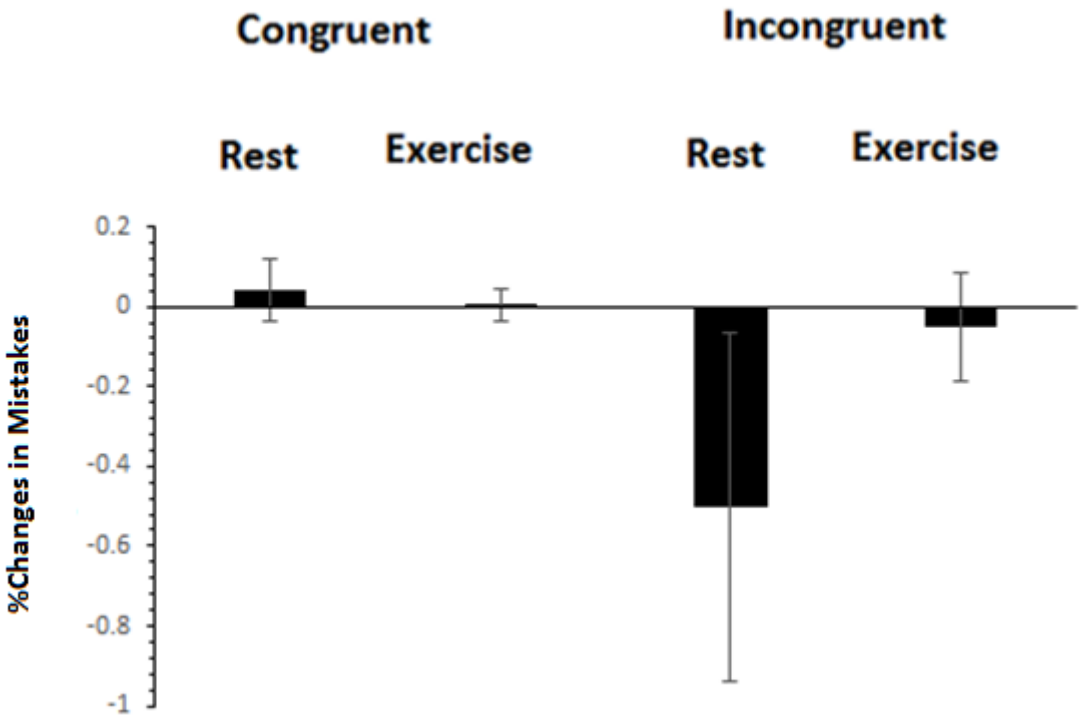


Figure 2.6. Percentage change in mistakes immediately after rest and exercise (represented by bar graphs of Means and S.E.) showed no significant changes.

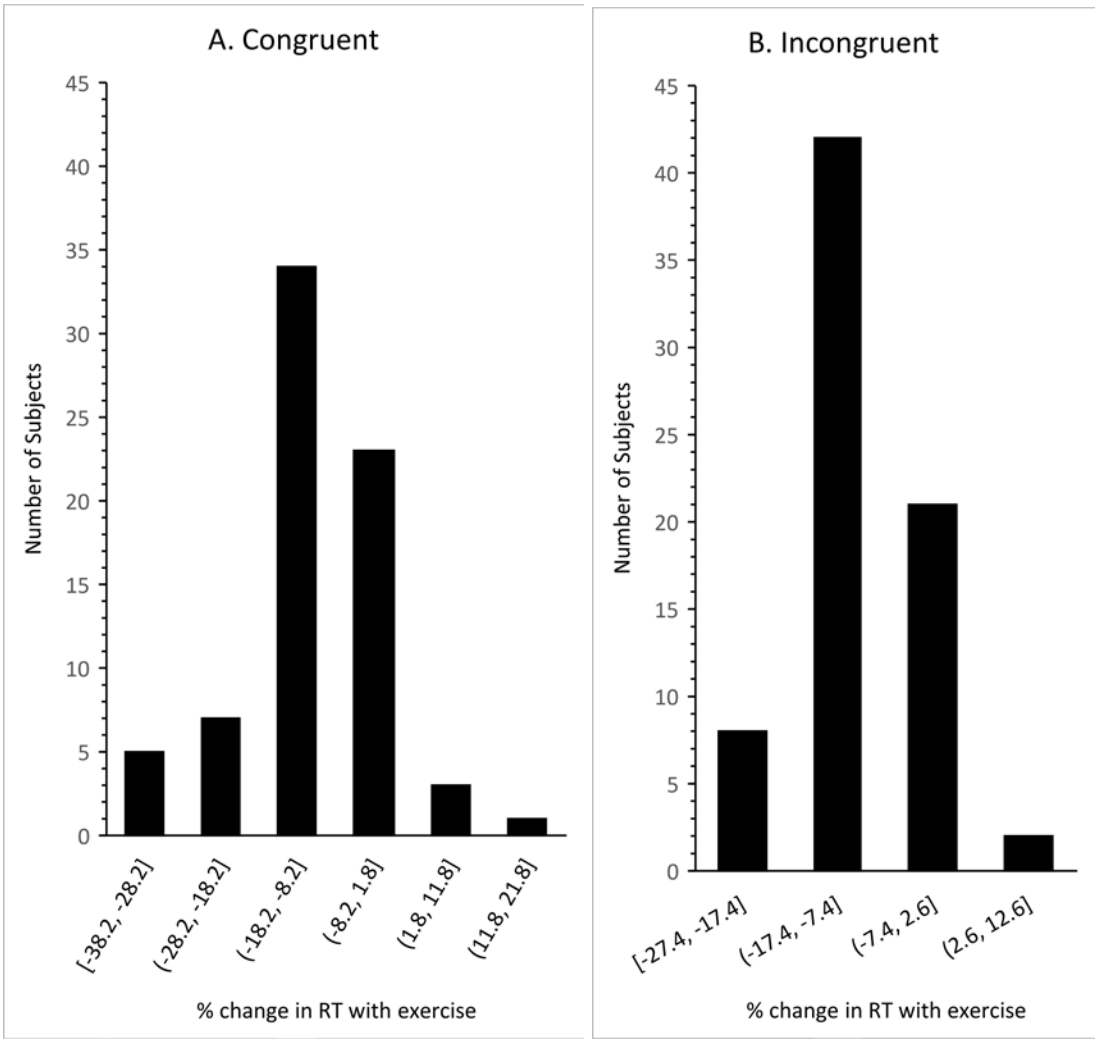


Figure 2.7. Histogram and box plots of RT changes immediately after exercise. The percentage changes in RT of congruent (A) and incongruent (B) Stroop tasks immediately after exercise for 73 subjects showed improvement (reduced RT meant improved processing speed). The X-axes were the range or bins of % changes in RT. (C) Boxplot of RT Stroop tasks. Change in RT immediately after exercise for congruent and incongruent Stroop tasks for 73 subjects. The % change in RT (congruent Stroop task) failed the Shapiro's normality test. In this box plot, the X represents the mean; the middle line in the box represents the median, the upper line of the box being the third quartile and the lower line the first quartile. The whiskers represent the maximum and the minimum.

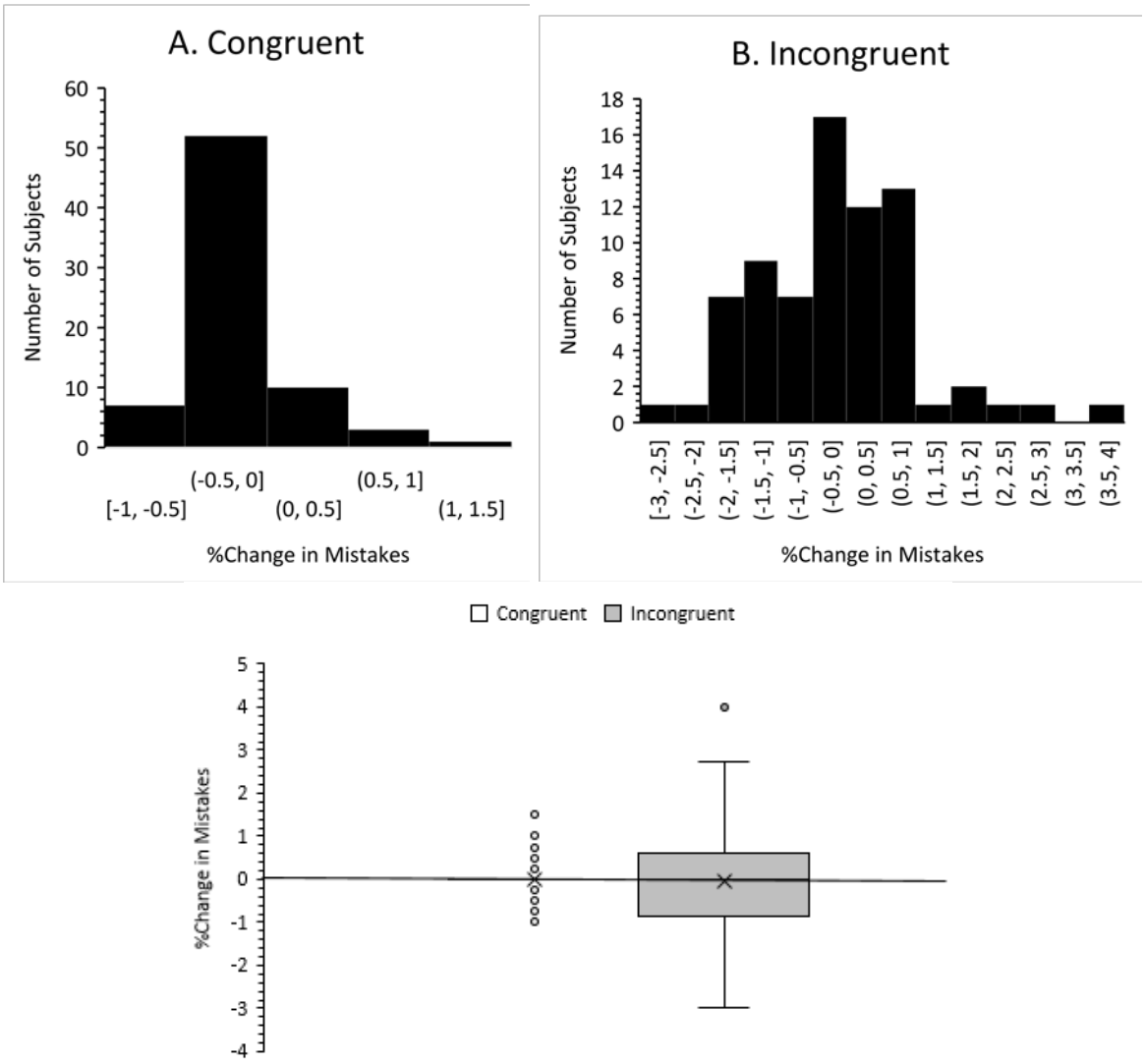


Figure 2.8. Histogram and box plots of mistakes rate changes immediately after exercise. See legend for Figure 2.6 for description of the plotting convention for box plots.

Table 2.3. Statistics of change in RT immediately after exercise for congruent and incongruent Stroop tasks. Values are Mean ± S.E. *** represents the significant p-values of <0.001 for the change immediately after exercise.

Change in RT immediately after exercise	Mean	Skewness	Kurtosis	Median	Normality test of Shapiro-Wilk, Significance value
				-9.99	p <0.05 (0.006) : so not normal distribution
Congruent	-11.41±1.07***	-0.51±0.28	1.83±0.55		
Incongruent	-9.48±0.8***	0.04±0.28	-0.14±0.55	-9.53	p >0.05 (0.84) :so normal distribution)

Table 2.4. Statistics of change in mistakes immediately after exercise for congruent and incongruent Stroop tasks. Values are Mean ± S.E.

Change in errors after exercise	Mean	Skewness	Kurtosis	Median
Congruent	0±.02	.75±.28	5.92±.55	0
Incongruent	-.02±.05	.48±.28	1.44±.55	0

2.9 Discussion

Subjects could become faster and make more mistakes (speed accuracy tradeoff) in general and that could mean an increase in automaticity without an improvement in cognition. Therefore, it was important to check accuracy in the behavioral data as well as speed. However, no correlation was seen between accuracy and speed when the tasks were repeated in the after sessions. In the before sessions and when the incongruent stimuli was present for the first time we did observe a positive correlation between speed and mistakes rate, which indicated no speed-accuracy tradeoff except for in the one subject at the before exercise condition (Figure 2.4). In general, subjects paying attention to the cognitive task made fewer mistakes and were faster. Thus, both speed and accuracy were important measures of cognitive performance in the Stroop tasks.

Reaction times became significantly faster in all subjects immediately after exercise (Figure 2.7), but there was no significant change in accuracy (Figure 2.8). Different human subjects performed differently in terms of accuracy especially for the incongruent Stroop task (Figure 2.8B). After exercise, several subjects made fewer mistakes, but some subjects made more mistakes. This could be attributed to differences in overall fitness and blood flow in terms of BMI and ADHD statuses. Subsequent analyses revealed the same. Overall, hypothesis H1A was supported that

in the pooled population only RT showed significant changes with exercise, but not accuracy.

Speed-accuracy correlation happened only for the novel incongruent Stroop tasks for both the before-exercise and the before-rest conditions, but not for the after sessions of rest and exercise. Since the speed-accuracy was positively correlated greater attentional resources were drawn to the incongruent Stroop and the subjects were focused on the task largely during the first exposure to the protocol, but that with practice they do not concentrate on the color-words as much. Initially with the first exposure, subjects who performed well in terms of speed also performed well in terms of accuracy. However, habituation made them faster at the incongruent Stroop task, but not necessarily more accurate. This was apparent irrespective of exercise or rest, simply as an outcome of practice. There were only one instance of a speed-accuracy tradeoff seen before exercise where a subject was fast but making a lot of errors (Boer & Keuss, 1982). For the easier familiar congruent Stroop tasks—not much attentional resources were required as the incongruent Stroop task, since there was no conflict between color and word. Subjects were almost always accurate and no correlation was seen between reaction time and number of errors. Hence, it was concluded that speed-accuracy correlations occurred only for the novel tasks. In addition, this finding stressed that to establish an improvement in executive function; one must demonstrate improvement in the accuracy rather than simply faster response times since both accounted for demonstrating better cognition. As accuracy did not seem to improve immediately after exercise as a population, we concluded that exercise did not improve executive function on a population basis since it only changed the RT but not the accuracy.

2.10 Conclusions and Future Directions.

Having shown that there is a population-wide improvement in the reaction time and not accuracy, we can correlate the changes to physiological factors like heart rate and brain hemodynamic response immediately after exercise in the future chapters. The current study has helped resolve the debate as to whether reaction time or accuracy improves in the Stroop task immediately after exercise.

The current study suggests that the use of mean as a measure of central tendency may not be appropriate for reaction time data. Instead, median is a better measure of central tendency for reaction time data as the distribution of RT is skewed.

With practice and irrespective of exercise or rest experiments, the speed-accuracy correlation for the cognitively challenging incongruent Stroop task disappeared as the subjects became more familiar with the incongruent Stroop task. Better speed was correlated to better accuracy, however, there was an instance of a participant who had a high speed but very low accuracy (speed-accuracy tradeoff) (Boer & Keuss, 1982); however in the general population that was not the case even if the experimenter instructed the subjects to go as fast as they could. This may indicate that humans have an inherent tendency to self-correct if they were really paying attention to the cognitive tasks.

CHAPTER 3

CARDIOVASCULAR PSYCHOPHYSIOLOGY AND EXERCISE

3.1 Heart Rate (HR) as Psychophysiological Measure

HR variability has been advanced as a psychophysiological measure of attention. HR changes have been identified as autonomic measures of visual attention and orienting reflex in infants, because the parasympathetic vagal nerve affected the heart rate correlates of attention (Richards et al., 1991). HR fell significantly during conflict-resolution decision making tasks in healthy adult controls compared to an adult group identified as alcoholic (Carmona-Perera et al., 2013). Somatic or bodily warning signals of slower HR came with risky decision making in normal adults. After punishment, HR slowed but, after reward, HR returned up to baseline levels (Crone et al., 2004). Using the Iowa Gambling Task, HR was predictive of decision making, in that HR decreased for disadvantageous trials compared to rewarding trials (Miu et al., 2008). Collectively, these data suggest that HR slows down with conflict-resolving decision making.

Typically, heart rate increases a sympathetic response to the physical stress of exercise (Laughlin, 1999). This increase contributes toward cardiac output increases, which can in turn maintain tissue oxygenation in the face of the increased oxygen demand in exercise (Pittman, 2011). This increase in HR after exercise may cause decision making and its accuracy to decline, because then the sympathetic responses challenge the inhibition-control mechanisms during the decision making tasks. Moreover, for subjects that have difficulty in inhibition control (e.g. ADHD subjects); the inhibition control can deteriorate after exercise, causing the subjects to make more mistakes in decision making. Speed of decision making may increase after exercise because of the sympathetic response, but this may have nothing to do with the

improvement in decision making, *per se*. In fact, an increase in speed testifies to an increased automaticity reflex.

3.2 HR, SO_2 and Breathing Rate (BR) Changes Immediately after Exercise

HR and BR are objective measures of cardiovascular changes after exercise (Fletcher et al., 1995). Increases in HR and BR after aerobic exercise are reliable markers of anaerobic thresholds of exercise intensity (Carey et al., 2005). The respiratory exchange ratio (RER) (carbon dioxide production divided by oxygen uptake) increases immediately after exercise intensity, but this RER increase is smaller in more fit subjects than in less fit subjects (Ramos-Jiménez et al., 2008). Thus, HR and BR could help us in studying the effects of altering the cardiovascular activity (including respiratory activity) on brain functions (Rattray et al., 2013).

The blood oxygen saturation level (SO_2) depicts the amount of oxygen bound by hemoglobin. In a healthy, normoxic population SO_2 is typically above 90% (Jubran, 2015). Immediately after exercise, the amount of carbon dioxide increases due to hyperventilation making the blood more acidic and this in turn may slightly lower SO_2 observed systemically and specifically in skeletal muscles, due to decreased affinity of oxygen to hemoglobin called the Bohr Effect (Mairbäurl, 2013; Braumann et al., 1982; Bauer, 1969). The blood oxygen saturation level SOmeasured by oximetry typically does not change more than 4% immediately after exercise in healthy population. Any change ≥4% was attributed to motion artifacts (Kist et al., 2002).

3.3 Correlations of Heart Rate with Behavioral Data

The dissertation hypothesis *H2* will be tested to achieve the objective of correlating HR changes during Stroop tasks with the behavioral data of reaction time

and accuracy changes immediately after exercise, along with comparisons with rest. The increased HR associated immediately after exercise was hypothesized to facilitate both speed and accuracy of Stroop tasks.

3.4 Methods

The overall research design was as presented in Figure 2.1. Essentially, HR was monitored during the Stroop tasks in all sessions. Additionally, BR and SO_2 were measured before and immediately following exercise. Figure 3.1 depicts the specific research design pertaining to the analyses done in this chapter.

Before the subject started exercise, BR, SO_2 and HR were recorded. BR, expressed as breaths/min, was calculated by asking the subject to count the number of outgoing breaths per 30 seconds while the experimenter kept the time using a stopwatch. To obtain the breathing rate, the experimenter doubled the 30 second rate. Heart rate in beats per minute (bpm), determined in each exercise trial, was monitored by a fingertip pulse monitor (Pulse Oximeter Easy Home, Medical LLC. (Model #. CMS50D1). In addition, using the same pulse oximeter the SO_2 was recorded before and immediately following exercise. HR was also monitored during exercise to determine if the subject was able to maintain the desired 70% increase in the maximal HR during the 30 minutes of exercise. Immediately after completion of the exercise bout, both HR and BR were recorded, and the changes compared to pre-exercise resting levels.

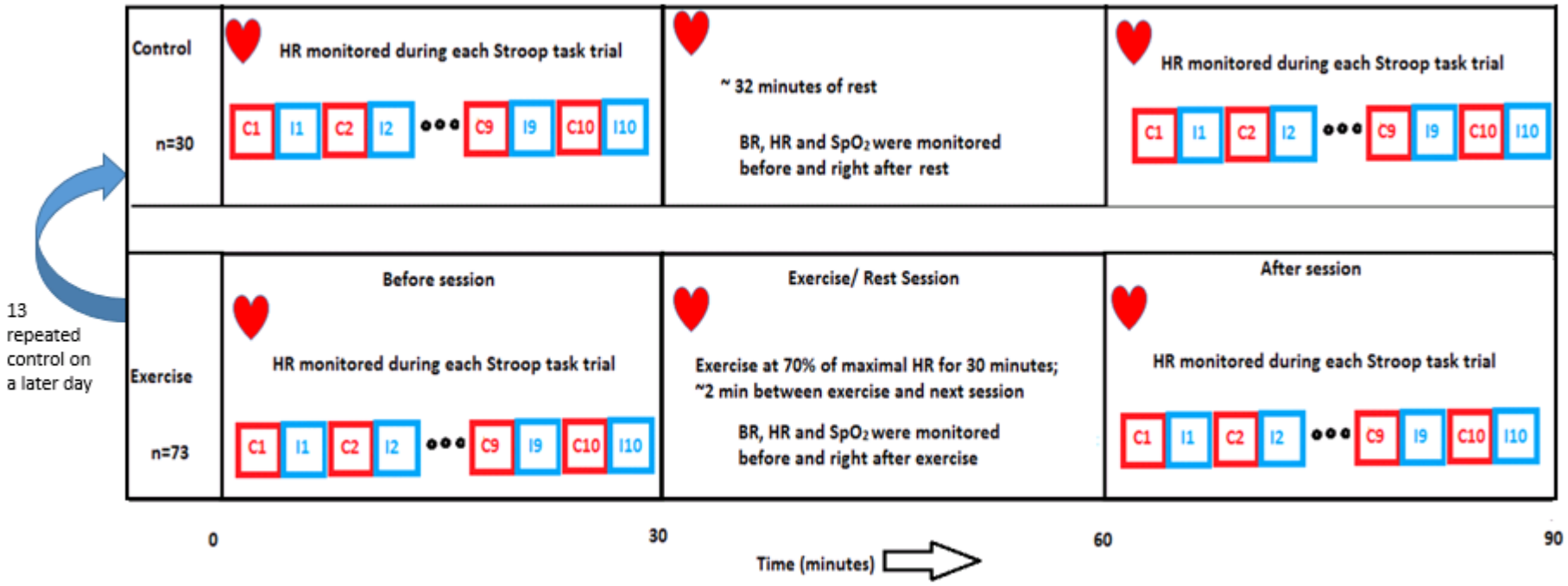


Figure 3.1. Cardiovascular psychophysiological measures in research design. Heart rate (HR) and breathing rate (BR) measures were analyzed at the points in time depicted in this figure. HR, SO_2 and BR were measured before and immediately following exercise. In addition, HR was measured during the Stroop task trials in both the before- and after-exerecise sessions.

3.5 Data Analysis Techniques

3.5.1 HR, SO_2 and BR, Before and Immediately Following Exercise

The distribution of HR, SO_2 and BR before and immediately following exercise was depicted using Box Plots. Normality tests were done on these parameters using Shapiro-Wilk tests in SPSS.

3.5.2 Change in HR, SO_2 and BR Immediately After Exercise and With Rest

The percent changes in HR, SO_2 and BR were described using descriptive statistics, bar graphs and box plots. The changes in these parameters were analyzed both immediately after exercise and with rest. In addition, the paired differences of these measures were checked for normality using Shapiro-Wilk test, using the software program SPSS, to determine whether parametric or non-parametric versions of paired t-tests would be appropriate for comparisons. Except for before exercise HR, all the other distributions were non-normal. Thus, non-parametric Wilcoxon-Signed Rank t-test was used for comparing the parameters.

3.5.3 % Change in HR Immediately After Exercise and Rest during Stroop Tasks

The % changes in HR during the Stroop tasks were plotted before and after exercise, and before and after the resting condition, to determine if there were significant changes. Data were assessed using non-parametric Wilcoxon-Signed Rank t-test (non-parametric version of paired t-tests) as the distributions of the data were non-normal and these were repeated measures.

3.5.4 Correlation of HR with RT and Accuracy

Pearson's correlation was used to correlate the relative % changes in HR during

Stroop tasks, with relative % changes in RT and accuracy during both congruent and incongruent Stroop tasks for the exercise experiment (n=73) and for the resting experiment (n=30). Pearson's Correlation was chosen because the comparisons were on normalized % changes and not on absolute changes.

A statistical technique called ecological validation was employed to determine whether the results were actually observed in at least one person. This technique is used for assessment of evidence-based intervention (Smith, 2012; Kazdin, 2010). Single subject data validation was done using Spearman's Ranked Correlation, a non-parametric version of correlation between HR and behavioral data.

All data are presented as means ± standard error, unless otherwise indicated.

3.6 Results

3.6.1 Distributions of HR, SO_2 and BR Before and After Rest (Control)

The distributions of HR, BR and SO_2 for before and after the rest condition are shown in Figure 3.2. The values for SO_2 were not normally distributed, before or after rest and stayed consistent around 97%. BR was normally distributed after rest, but before rest, there was a non-normal distribution with several outliers. This indicated that the subjects could have had differential BR based on their cognitive and emotional experiences before rest. However, after rest BR was approximately 20 across the population. With rest, only HR decreased significantly ($p<0.01$). BR and SO_2 did not change significantly ($p>0.05$), indicated in Figure 3.2. The percentage changes were in Section 3.6.3.

3.6.2 Distributions of HR, SO_2 and BR Before and After Exercise

The distributions of HR, BR and SO_2 for before and after exercise are shown in

Figure 3.3. Before exercise, the HR was normally distributed. However, after exercise the HR distribution had a positive skew, with values of 84±2 beats per minute before exercise, compared to 136±2 beats per minute after exercise. The BR was not normally distributed before or after exercise and had a negative skew for both distributions (Figure 3.3). This indicates that most breathing rate (respiratory rate) was similar across individuals and was 20±1 breaths per minute before exercise (resting level), and increased to 30±2 breaths per minute (exercise level). The SO_2 was not normally distributed, before or after exercise, and stayed consistently at around 98.25 % ± 0.34 before exercise and 96.95% ±0.17 after exercise. Immediately following exercise, all the three parameters of HR, BR and SO_2 differed significantly (p<0.001) from control values, using the non-parametric Wilcoxon signed rank tests (Figure 3.3).

3.6.3 % Changes in HR, SO_2 and BR After Exercise Compared to Rest

Percentage changes in HR, BR and SO_2 after exercise compared to rest are depicted in Figure 3.4 as boxplots. BR increased significantly (p<0.001) after exercise by 38%. HR also showed a significant (p<0.001) increase of 68% immediately after exercise and SO_2 showed a significant (p<0.001) decrease of 1.2%. Compared to change with rest, HR and BR changes immediately after exercise were significantly higher, (p<0.001) at 67% and 37%, respectively. SO_2 was significantly lower (p<0.05) by 1.6%immediately after exercise compared to rest.

3.6.4 HR Changes during Stroop Tasks Immediately After Exercise and With Rest

HR showed a significant increase (p<0.001) of approximately 15% in 73 subjects during both congruent and incongruent Stroop tasks when comparing pre- and post-exercise (Figure 3.5). HR showed a significant decrease 5% (p<0.001)

(n=30) in resting controls, a value also evident for individuals who had practiced, for both the incongruent and congruent Stroop tasks. The changes in %HR immediately after exercise were 20% higher (p<0.001) compared to control. HR with rest or practice or control was 5% lower (p<0.001).

3.6.5 Correlation of HR and Behavioral Data Immediately After Exercise

The % HR changes during the incongruent Stroop task performances were negatively correlated (p<0.01, n=73) with % RT changes during the incongruent Stroop tasks immediately after exercise (Figure 3.6 A). However, there was no significant (p=0.93) correlation between these two factors for the resting (control) experiment (n=30). In addition, there was no significant correlation (p=0.93 for congruent, p=0.87 for incongruent) between HR and RT changes for the congruent Stroop tasks.

The % HR changes during the incongruent Stroop tasks were negatively correlated (p=0.05, n=73) with the % changes in the mistakes rate for exercising individuals (Figure 3.6 B). There was no significant correlation (p>0.05) for the resting control individuals (n=30). In addition, there was no significant correlation (p>0.05) between changes in HR and error (mistakes) for the congruent Stroop tasks.

Furthermore, pooling the Spearman's ranked order correlation coefficients (Rho) for each of the 73 subjects and then comparing the before and after exercise sessions using RM-ANOVA (not displayed) revealed the same outcome as the regression analyses (Figure 3.6).

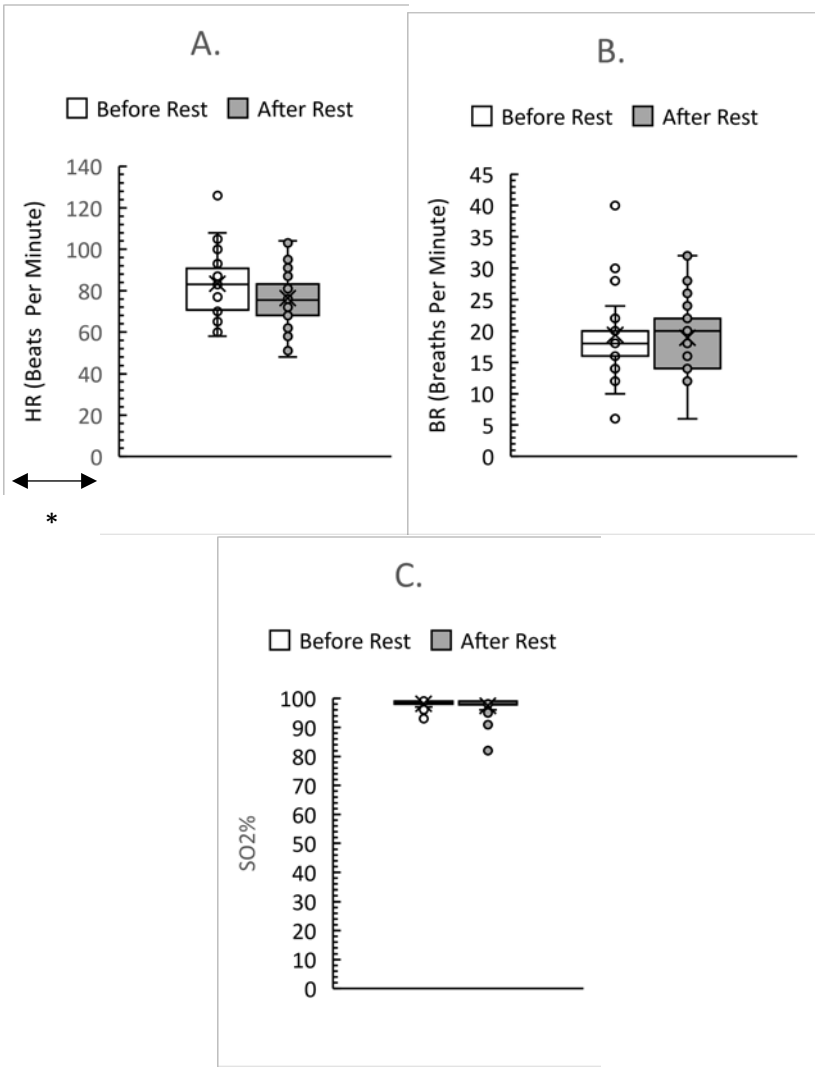


Figure 3.2. Distributions of HR, BR and SO_2 for rest (controls). HR normally distribution before and after rest (A), BR was not normally distributed before rest, but BR normally distributed after rest (B), and the SO_2 was not normally distributed before or after rest (C). With rest, HR significantly *, $p<0.05$ decreased; however, the BR and SO_2 did not change significantly.

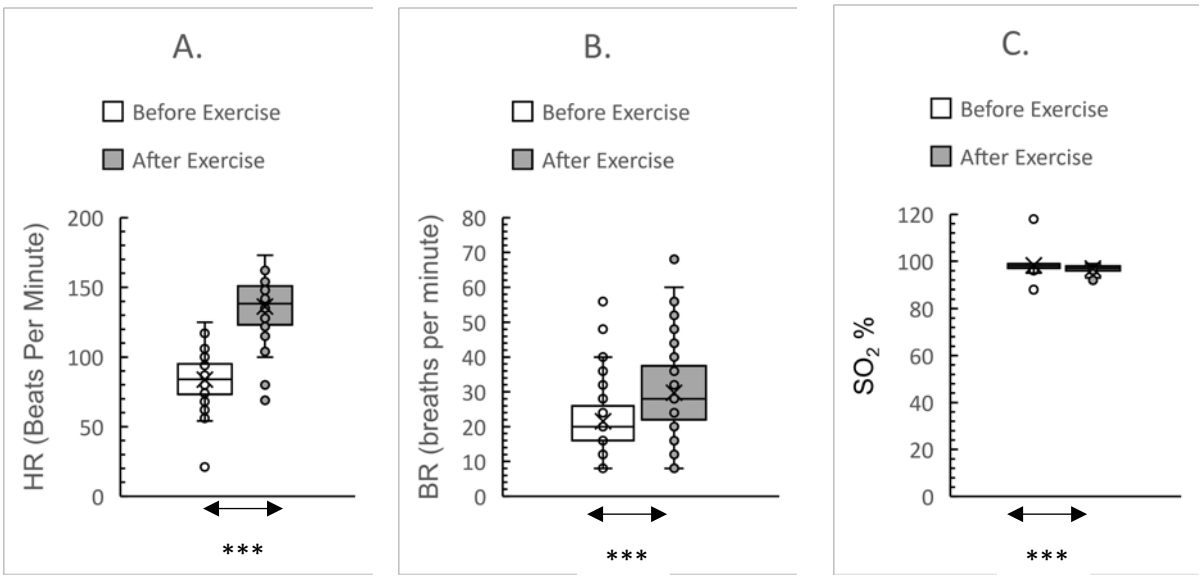


Figure 3.3. Distributions of HR, BR and SO_2 for exercise experiments. Except HR (A) for the before exercise condition, HR after exercise (A), BR before and after exercise (B) and, SO_2 before and after exercise (C) were non-normally distributed per Shapiro-Wilk test. Immediately after exercise, HR and BR values showed significant ***, p<0.001 increases and PO_2 showed significant *, p<0.001 decreases.

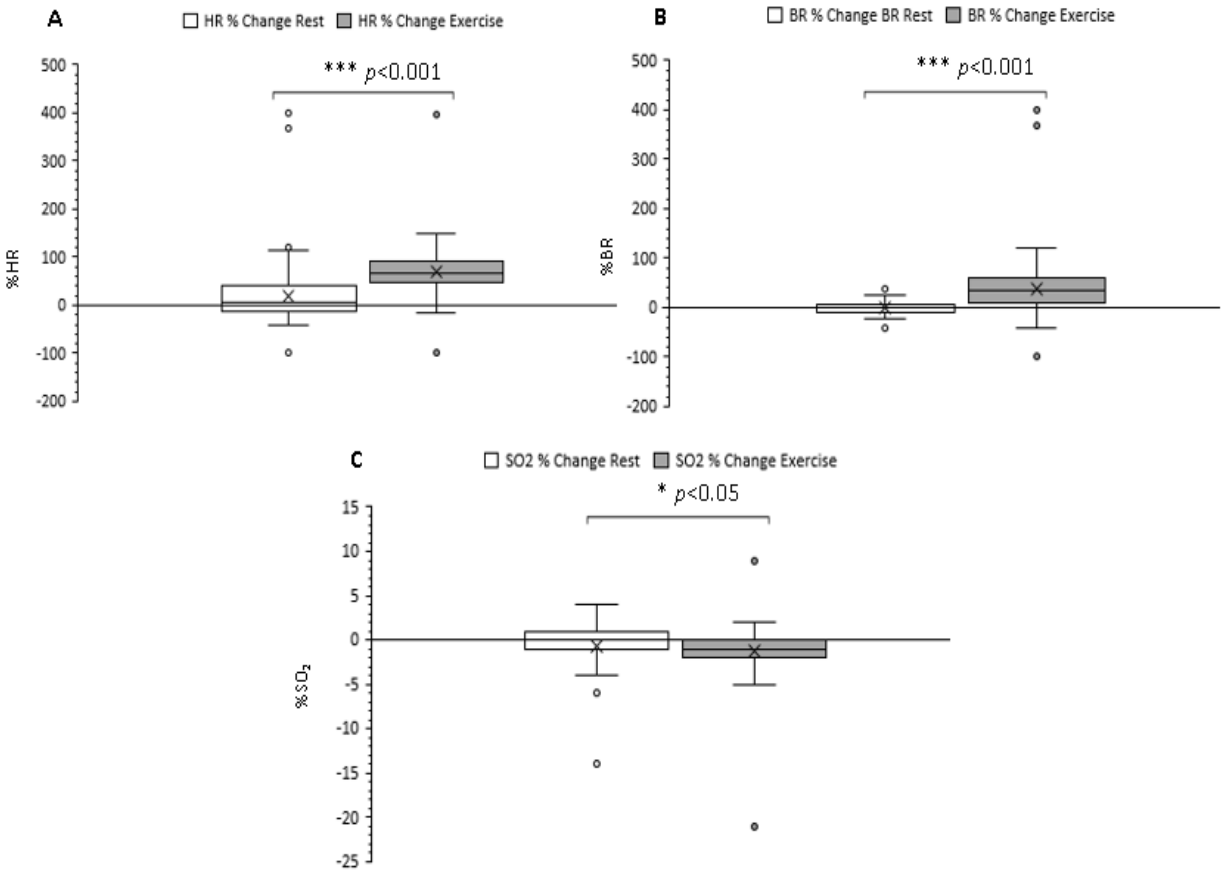


Figure 3.4. Distributions of change in HR (A), BR (B) and SO_2(C) immediately after exercise and immediately after rest. All three parameters differed significantly between the exercise and rest experiments. * p<0.05, *** p<0.001.

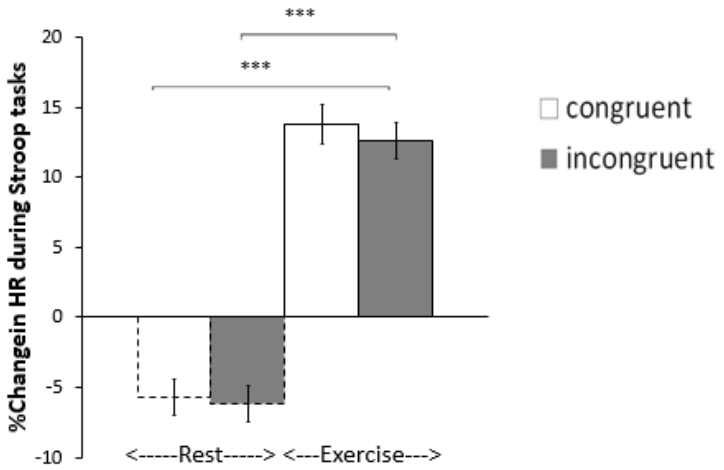


Figure 3.5. Percentage HR changes during the Stroop tasks before and after exercise. Values shown are means ± 1 standard error. ***, $p<0.001$

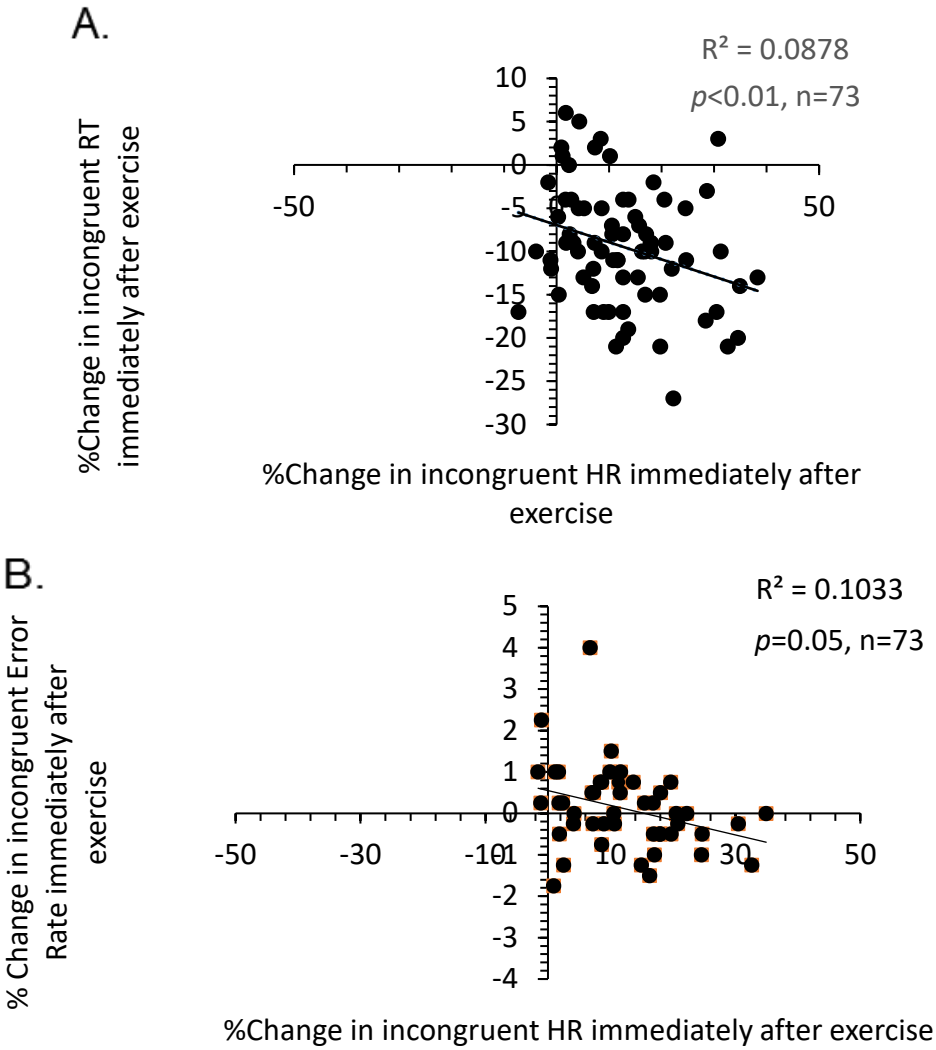


Figure 3.6. HR change correlations to behavioral data changes in incongruent task immediately after exercise, group data. A. % RT vs. % HR; B. % Mistakes rate vs. % HR.

3.7 Discussion

This study has first shown that heart rate and breathing rate increased immediately after exercise and blood oxygen saturation decreased. The increases in heart rate and breathing rate immediately after exercise were indicative of sympathomimetic stimulation (Fletcher et al., 1995). Increases in these parameters were attributed to higher ventilation rates and exercise intensities (Carey et al., 2005).

In addition, we know that higher ventilation rates and higher exercise intensities decreased cognitive functioning (Ogoh et al., 2014; Konishi et al., 2017). Thus, the higher HR and BR immediately after exercise could have compromised the cognitive functioning of some participants.

The Breathing Rate is typically about 20 breaths per minute in resting adult healthy population (Braun, 1990). In addition, immediately after exercise BR increases up to 30 breaths per minute (Carey et al., 2005). Our findings support the expectation of about 20 breaths per minutes before exercise and 30 breaths per minute after exercise. The SO_2 was not normally distributed before or after exercise, or before and after rest That was expected because in normal humans, the SO_2 values stay between 90-99% (Jubran, 2015). The inter-subject variability in HR immediately after exercise seen in Figure 3.4 could be ascribed to different fitness levels in terms of BMI or respiratory fitness. This could also be an indication that some subjects did not exercise up to the mandated 70% of maximal heart rate level, although the mean change was approximately 68%, indicating that most did have about a 70% change in HR immediately after exercise. Immediately after exercise compared to rest controls, the HR and BR increased and the blood oxygen saturation percent or SO_2 showed decreases as expected.

There were increases in HR during the Stroop tasks after exercise that were

not seen just with practice. In fact, with practice heart rate slowed down, as evidence of conditioning to the experiments. This phenomenon has also been reported for orienting reflexes, where the experimental subject holds their breath to better attend to the decision making stimulus (Carmona-Perera et al., 2013; Crone et al., 2004; Miu et al. 2008). These findings could be explained by decision making being involved with inhibition control and activation of the parasympathetic system and eventually slowing of the heart rate (Herman et al., 2009; Neil-Dwyer et al., 1981).

The increase in heart rate after exercise correlated negatively with reaction time and number of errors for the incongruent task. Collectively, these data supported my hypothesis *H2* that changes in executive function could be an outcome of cardiovascular changes induced by exercise related physiological arousal (Rattray et al., 2013).

Important to note is that heart rate is not necessarily directly proportional to cardiac output (heart rate × stroke volume). Cardiac output matches with the astrocytic, inter-neuronal and neuronal activities (Woolsey et al., 1996). In the present study, the slowing down of HR could cause reduction in cardiac output, which in turn might lower the activation (i.e. inhibition) of certain neurons required for effective decision making in the control experiment (Figure 3.5). Yet, after a single bout of exercise, an opposite sympathomimetic response occurs with increases in HR and BR (Figure 3.4). This increase in sympathetic response might compromise the attention-orientation reflex by reducing the inhibitory neuron activity or it might improve the cardiac output and improve executive function.

In conclusion, HR decreased with practice and this was attributed to the habituation of the Stroop tasks. However, immediately after exercise the HR increased and this increase continued during the Stroop task responses recorded after exercise.

The increase in the HR immediately after exercise did correlate with the faster RT and also better accuracy immediately after exercise for the incongruent Stroop task indicating that blood flow) or oxygenated blood perfusion could contribute to improvement in executive function.

3.8 Future Studies

Important to note is that changes in HR are not equivalent to changes in the cardiac output (cardiac output = Heart Rate X Stroke Volume) (Lee & Oh, 2016). Nor are changes in cardiac output directly correlated with changes in the neural activity, although there were evidences of neurovascular coupling (Woolsey et al., 1996). Consequently, future studies should involve measurement of brain blood flow to further support the hypothesis of metabolic impacts on cognition immediately after exercise and specifically the correlations of brain hemodynamic data with behavioral data (*H4*, section 1.9).

CHAPTER 4

EXERCISE ON BRAIN HEMODYNAMICS DURING COGNITION

4.1 Introduction

4.1.1 Theories of Cerebral Hemodynamics

4.1.1.1 Regional Perfusion- Oxygen Partial Pressure

The term “cerebral hemodynamics” describes the relationships and interactions of blood flow, delivery and extraction of oxygen according to metabolic demand. Oxygen partial pressure drives oxygen molecules into the metabolizing brain tissues along a partial pressure gradient. This regional diffusion can change to meet the increased metabolic demand that might result from higher neural activities. During a task involving cognition, or any other measurable activities, the brain can be recorded ‘functionally’ during the task. Regional blood flow changes occur during the ‘functional’ task and these changes are likely accompanied by vasodilation (increased diameter, resulting in increased volume) of blood vessels, leading to the phenomenon of functional hyperemia. Functional hyperemia is a term that describes how brain modulates the increased cerebral blood flow (with oxygen and nutrients) with increase in intracranial oxygen partial pressures to fuel the intense neural activities in excess of metabolic demands. These changes are known to correspond to cognitive activities as well (Otsu et al., 2015; Vazquez et al., 2010; Woolsey et al., 1996). The mechanism for regional blood flow changes involves nitric oxide and byproducts of metabolism, such as hydrogen ions, oxygen, potassium ions that may cause dilation of cerebral blood vessels (Yang & Liu, 2017; Vavilala & Soriano, 2011; Attwell et al., 2010). This intricate balance appears to be controlled by glial (astrocyte) and neuron regulation (Yang & Liu, 2017; Otsu et al., 2015; Vavilala & Soriano, 2011; Attwell et al., 2010). Another potential mechanism that might lead to vasodilation and increased cerebral

blood volume is hypercapnia (increased arterial carbon dioxide) (Yang & Liu, 2017; Otsu et al., 2015; Peterson et al., 2011), which can happen during and right after exercise and also with anxiety (Ogoh et al., 2014; Bechbache et al., 1979).

4.1.1.2 Cerebral Blood Flow Autoregulation

Overall, the body does not greatly change blood hydrostatic pressure, even immediately after exercise. What does change is blood perfusion - the flow of blood through the tissues to maintain an adequate oxygen partial pressure gradient for oxygen diffusion into the brain tissues. Cerebral autoregulation is a blood flow mechanism that by virtue of which total cerebral blood flow (CBF_{tot}) is maintained constant even as arterial oxygen partial pressure (and the associated oxygen partial pressure gradient) changes. Cerebral autoregulation is an important step in maintaining constant energy substrates for critical brain processes (Yang & Liu, 2017; Fantini et al., 2016; Prabhakar et al., 2014; Paulson et al., 1990). The concept of the cerebral autoregulation of blood flow applies to the whole brain tissue and is not to be confused with the regional brain perfusion.

4.1.1.3 Supply vs Demand Concept of Cerebral Metabolism

During and immediately after exercise, capillary recruitment (an increase in the number of perfused capillaries) occurs in the skeletal muscles (Fry et al., 2013; Honig et al., 1980). However, in the there no capillary recruitment is found using direct observation of movement of RBC through capillary bed (Jespersen & Østergaard, 2012; Secher et al., 2008; Gjedde & Kuwabara, 1993). Increased brain metabolism immediately after exercise depends upon an enhanced gradient for oxygen diffusion, since there is no capillary recruitment in the brain. During strenuous exercise, cerebral

oxygenation decreased due to hyperventilation-induced arterial desaturation (Jespersen & Østergaard, 2012; Secher et al., 2008). The work of Roy & Sherrington (1890) first opened up the concept of “neurovascular coupling” - the changing of arterial tone with changing metabolic needs. The assumption that immediately after exercise there was an enhanced gradient for oxygen diffusion follows from the Fick’s principle applied to matching oxygen supply with oxygen demand (Pittman et al., 2011) Equation 4.1:

$$\dot{V}O_2 = Q\,\{[O_2]_{in} - [O_2]_{out}\} / [O_2]_{in}$$

where, $\dot{V}O_2$ is the oxygen consumption (demand), Q $[O_2]_{in}$ represents the oxygen delivery (supply of CBF) via the convective transport of oxygen through arterioles), $\{[O_2]_{in} - [O_2]_{out}\} / [O_2]_{in}$ represents oxygen extraction capabilities in capillaries. Oxygen demand depends upon metabolic rate of the perfused tissue, while oxygen delivery is dependent on the vascular oxygen supply. The Q term incorporates the surface area, thickness and diffusion coefficient aspects of Fick’s law equation. Thus, brain brain flow rate is impacted more by these factors represented by Q. The brain is one of the organs that is highly vascularized with greater surface area compared to many other tissues. Therefore, Pittman et al. (2011) concluded that oxygen demand depends on the oxygen supply via diffusion (irrespective of the oxygen extraction capabilities) and driven by the oxygen partial pressure gradient of between blood and cells.

4.1.2 Neurovascular Coupling in Brain Tissue

Neuronal activities include ion fluxes across the neuronal membrane, second messenger cyclic AMP activity, glucose and oxygen consumption, rise in local lactate concentration, redox state of intracellular NADH and cytochrome oxidase, local arterial

vasodilation, and consequent increases in regional cerebral blood volume (CBV) and regional CBF (Yang & Liu, 2017; Jespersen & Østergaard, 2012; Radak et al., 2007; Villringer & Chance, 1997). Irrespective of the local oxygen consumption, there was a further increase (compared to the immediate functional needs of the cell) in CBF and oxygen delivery. This causes cerebral blood oxygenation to rise locally in response to the stimulus, which could be cognitive stimulus (Yang & Liu, 2017; Jespersen & Østergaard, 2012; Vazquez et al., 2010). Metabolic activity in the brain during excitation and conduction of the electrical signal involves the active transportation of ions to maintain and bring back the membrane potentials that were discharged (Yang & Liu, 2017; Jespersen & Østergaard, 2012; Radak et al., 2007; Villringer & Chance, 1997). Different regions of the brain have different energy requirements depending on the different levels of neuronal activity in the brain (Yang & Liu, 2017; Jespersen & Østergaard, 2012). Thus, the amount of blood flow is related to the neuronal activity of that tissue. The functional activation is accompanied by the rise in regional cerebral blood flow when presented with a specific task stimulus. This is referred to as neurovascular coupling (see above). During functional activation of neurons, oxygen metabolism increases due to the cognitive task load, and this increase in oxygen consumption is due to the increased neuronal activities. One consequence can be a temporary decrease in brain tissue oxygenation, as well. When the impact of the stimulus is longer term, glucose and oxygen consumption are kept constant by increasing the capillary density (capillary recruitment). In turn, neural activation will require increased CBV and CBF, reflecting neurovascular coupling.

When stimuli are short-term, the metabolic and hemodynamic changes of brain tissue are likely to operate differently. When oxygen demand is high and the supply not commensurate for the cognitive task load, then it has been predicted that the

deoxy-Hb will be transiently high and then dip as the oxygen level increases in the global cerebral blood circulation (Mangia et al., 2009). Thus, the cerebral hemo-"dynamics" involve constant fluctuation in blood flow in response to activities example cognitive activities.

4.1.3 Functional Near Infrared Spectroscopy (fNIRS) Data

Optical brain imaging technology measures the blood flow changes in the superficial cortical areas of the brain. Functional near-red infrared spectroscopy (fNIRS) measures the oxyhemoglobin (oxy-Hb) concentration and deoxyhemoglobin (deoxy-Hb) concentrations in blood flowing through the brain tissue (Plenger et al., 2016; Tam & Zouridakis 2014; Yamada et al., 2012). Jobsis (1977) is known as the initiator of NIRS. The Imagent (2005) fNIRS equipment used for the current study was a continuous wave fNIRS system that produced relative measures of oxy- and deoxy-Hb concentrations. Since it was more important to statistically significantly detect a change in brain activity rather than quantify it absolutely, relative measures were enough (Scholkmann et al., 2014). The optical basis of fNIRS measurements depends upon the fact that hemoglobin molecules in blood scatter infrared light. Importantly, the degree of light scattering is proportional to the hemoglobin concentration, which can be correlated with the relative amounts of oxy and deoxy-Hb molecules (Plenger et al., 2016; Tam & Zouridakis 2014; Yamada et al., 2012). The light frequencies at infrared and near-infrared wavelengths are used to differentiate the relative levels of oxy-Hb and deoxy-Hb. In this technique, infrared light is directed into the tissue by fibre-optic bundles called optodes (emitters). A second set of optodes (detectors) collect light after the light has passed through the tissue (Tam & Zouridakis 2014; Villringer & Chance, 1997). Typically, the emitters

and detectors are usually on the wearable headcaps (Tam & Zouridakis 2014; Villringer & Chance, 1997). Increases in number of source-detector distances enabled higher depth sensitivity upto the level of detection in sulcal folds (Scholkmann et al., 2014). The modified Beer-Lambert law (*Equation 4.2*) is used to calculate the absorption and scattering of light through the brain tissue (Butti et al. et al., 2007). After filtering the raw data to remove cardiac oscillations, intensity I (t) for each channel is converted to optical density OD changes using the following equation of modified Beer-Lambert Law (Scholkmann et al., 2014) (Schytz, et al., 2009) (Delpy et al., 1988).

Equation 4.2:
ΔOD: ΔOD (t) =−ln [I (t)/I (baseline)] = [specific molar extinction coefficient X change in chromophore concentration X distance (width of cuvette) X differential path length factor] + (signal loss due to light scattering)

The signal loss due to light scattering factor is considered time-invariant assuming the change in light scattering is small compared to the change in absorption.

fNIRS gives insight into the metabolic rate of the cortical pyramidal neuronal (that relay information in the brain) through the hemodynamic changes in the prefrontal or motor cortices (Plenger et al., 2016; Tam & Zouridakis 2014; Yamada et al., 2012; Merzagora et al., 2009). Oxyhemoglobin refers to the Relaxed or R-state Hemoglobin whose allosteric confirmation allows binding to four oxygen molecules, and this is usually seen in the arterial blood, capillaries and less often in the venous blood. Due to a cooperativity effect, when oxygen molecules start disassociating, one oxygen molecule unbinds followed by the next. Eventually all oxygen molecules have unbound from the hemoglobin molecule, taking the hemoglobin to the tensed or T-state (which is the default state). This T-state hemoglobin is what is referred to as deoxy-Hb. In fNIRS, the detected oxy-Hb corresponds to the amount of oxygen delivered to the brain. The deoxy-Hb corresponds to the amount of oxygen utilized by the brain. Thus,

oxy-Hb is more indicative of cardiovascular performance and deoxy-Hb is more of a neuronal or metabolic activity measurement.

If neuronal activity increases after exercise, oxygen extraction will increase. This means that the deoxy-Hb should go higher and the oxy-Hb or the delivery may not keep up with this oxygen demand, given that the limited metabolic resources are also going to the high-performing muscle tissues (Tam & Zourdakis, 2014). We can rule out cardiovascular effects of an acute bout of exercise working with two other derived physiological variables - total hemoglobin or total-Hb (summation of oxy and deoxy-Hb), and the difference in the oxy and deoxy-Hb (diff-Hb). The total-Hb concentrations account for all hemoglobin in the blood and is thus correlated with blood perfusion of oxygen. Diff-Hb approximates the amount of oxygenation (or oxygen utilization) in cortical brain tissue (Tam, 2013).

Brain activation using the fNIRS technique is deduced from an increase in oxy-Hb and a simultaneous decrease in deoxy-Hb during an excitatory cognitive task (Schecklmann et al., 2008). The cardiovascular response followed the neuronal activity. The signal peak occurs in the signal if the effect of the brain activation lasts longer. On the other hand, brain activity changes could also return to the baseline at the end of the task when the functional hyperemia is absent (Minati et al., 2011). However, there could be situations where neural activation increases, and the subsequent challenges of physical exercise causes a further burden on the finite metabolic resources. This in turn may compromise brain executive functions such as decision making.

The present study has quantified changes in hemodynamic measures in response to cognitive stimuli to determine if hemodynamic changes are cardiovascular in nature or related to metabolic neural activity. This study has included the variables

of gender, BMI and ADHD - variables that influence cognition differently in different populations to quantify the uncoupling effects of PFC cortical hemodynamics immediately after exercise. Based on the above literature review, it was predicted that cardiovascular changes (*H3B, section 1.9*) would occur at motor cortex and prefrontal cortex.

4.1.4 fNIRS and Stroop Tasks

To show if hemodynamic changes during the Stroop task correlate to changes in behavioral data, we need to establish correlations in the before exercise conditions. fNIRS technology has been widely used for quantifying Stroop task response in the brain (Plenger et al., 2016; Tam & Zouridakis 2014). Usually neuroimaging analyses report 'functional' changes to RT data or mistakes data, based on circumstantial changes in hemodynamics, which could have also been due to systemic changes un-related to cognition (Lambrick et al., 2016, Byun et al., 2014). Thus, the current study used the approach of correlating the non-parametric behavioral data with parametric hemodynamics data using non-parametric Spearman's ranked correlation (Liu et al., 2016; Mukaka, 2012). Although population wide, RT changed immediately after exercise and not accuracy (Chapter 2), it was important to correlate the hemodynamic data to both RT and accuracy to understand the exercise physiology-based hemodynamic impacts on cognition (*H3B*, section 1.9). In addition, it was also important to determine if demographics impacted the correlation between exercise physiology-based hemodynamics and cognition (*H3C*, section 1.9). The overall research design of this chapter was depicted in Figure 4.3.

4.1.5 Blood Flow in the Brain during Stroop Tasks after Exercise

Global cerebral circulatory condition has been measured by the cerebral blood flow (CBF) at the middle cerebral artery. Blood flow in this study was not correlated with improvement in post-exercise cognitive functioning (decision making) (Ogoh et al., 2014). As a control used in that study, hypercapnia produced by carbon dioxide inhalation induced an increase in global CBF. However, this increase in blood flow did not affect either speed or accuracy of decision making tasks used by Ogoh et al., (2014). Global cerebral blood flow remained constant (supporting cerebral autoregulation) when subjects conducted Stroop tasks during and after exercise (Lucas et al., 2012). These authors also reported that the regional cortical hemodynamics at the PFC were correlated to cognition, at least before exercise, but that these regional cortical hemodynamics became uncoupled immediately following exercise (Lucas et al., 2012).

The study by Lucas et al. (2012) was extremely helpful to brain researchers, contributing to our understanding of the cortical hemodynamic effects of exercise and, importantly, its correlations with Stroop task speed and accuracy. With moderate intensity exercise (30% of maximal heart rate) [Note: refer to section 2.7.4 for the explanation on exercise intensity level]. The deoxy-Hb at the right PFC, indicative of regional blood flow, reflects oxygen extraction by the neural tissue, which increases from the resting levels. However, at 70% of maximal heart rate, deoxy-Hb levels returned towards, but did not fully reach, resting baseline levels. This indicates that oxygen extraction has a capacity or limit and that there cannot be additional oxygen extraction beyond that limit. Oxy-Hb usually has the opposite response to deoxy-Hb, in that there was an initial decrease for up to 30% of exercise intensity and then a gradual increase for up to 70% at the PFC (Lucas et al., 2012). This supports the

hypothesis that heart rate and corresponding cardiac output increase lead to greater oxygen delivery immediately after exercise. A pattern of increased regional cerebral neural activation was evident from an increase in regional cerebral uptake of oxygen (Lucas et al.,2012). Oxy hemoglobin was also observed after exercise by the apparent local rise in CBF in excess of oxygen demand was attributed to higher cardiac output post submaximal exercise (Ide et al., 2000).

The cortical hemodynamics of oxy, deoxy and total-Hb have also been correlated with speed and accuracy of performing the Stroop task (Lucas et al., 2012). Immediately following exercise the cortical hemodynamics became uncoupled from the cognitive parameters of speed and accuracy. Initially, at 30% exercise intensity, subjects made more errors (maybe a sympathetic response). However, at 70% exercise intensity, subjects made fewer errors compared to resting baseline, both for the congruent and incongruent Stroop tasks. Overall, the initial effects of exercise caused the uncoupling of the cortical hemodynamics from the cognitive parameters of speed and accuracy. This effect was moderated only if there was enough oxygen delivery during the course of exercise. In addition, if exercise became too difficult or at a supramaximal intensity, then the exercise bout could result in poorer performance in Stroop tasks (Ogoh et al., 2014).

All three variables of oxy, deoxy and total-Hb collectively explained the variance in the Stroop performance, with total-Hb or total perfusion accounting for the highest variance (38%) (Lambrick ete al., 2016). These authors concluded that the increase in oxygenation of the prefrontal cortex after exercise contributed to higher executive function. Oxy-Hb was recorded at a higher level during the incongruent Stroop task compared to the congruent Stroop task, when measured bilaterally at the frontal lobes (dorsolateral PFC). These changes were correlated with higher attention towards the

incongruent Stroop task stimuli, requiring inhibition of the unwanted response (Plenger, 2016). In addition, higher oxy-Hb occurs at the left somatosensory and motor cortices, values apparently correlated with the act of vocalizing the responses during performance of the Stroop tasks (Plenger et al., 2016). After an acute bout of 10 minutes of mild exercise at 30% maximal heart rate, fNIRS revealed higher cortical activations in terms of higher oxy-Hb (with no significant deoxy-Hb changes) evoked in the left DLPFC and left frontopolar regions (Byun et al., 2014). With an acute bout of exercise at 50% of maximal heart rate, subjects showed an increase in oxy-Hb but not deoxy-Hb at the left dorsolateral PFC (Yanagisawa et al., 2010). However, in another study, acute exercise with progressively higher exercise intensities (52%, 68%, 84%) increased both oxy and deoxy-Hb (overall oxygenation) at the PFC (Giles et al., 2014). In children aged 8-10 years involved in moderate intensity aerobic activity, both oxy-Hb and total-Hb increased post-exercise, corresponding to improvement in executive function evident from improved Stroop performance (Lambrick et al., 2016).

Based on the above literature review, it was predicted in Hypothesis *H4B* (section 1.9) that only the oxygenated blood perfusion variable (and not the neural activity predictor of oxygen extraction variable) would correlate with the behavioral data changes immediately after exercise. It was further hypothesized that demographics would moderate the correlations (*H4C*, section 1.9).

4.2 Methods.

4.2.1 Hemodynamic Recording using fNIRS

Hemodynamic (blood oxygenation) data of both oxy-Hb and deoxy-Hb levels were recorded from the prefrontal cortex (PFC) and motor cortex (MC) of the dominant

hemisphere while the subjects performed the Stroop tasks and as depicted in Figure 4.3. Recording locations are depicted in Figure 4.1.

4.2.2 fNIRS Equipment and Associated Software

The fNIRS equipment used in this study was manufactured by Imagent™ (Champaign, IL) which recorded the changes in the fast optical signals (time scale > 100 ms) due to the local variations of the oxy-Hb and deoxy-Hb concentrations. Imagent™ fNIRS equipment uses the Boxy software that calculates the concentration levels of oxy and deoxy-Hb based on the modified Beer-Lambert Law (Imagent et al., 2005, Equation 4.2). By flashing infrared light at the alternate wavelengths, the relative measures of the oxy and deoxy-Hb absorption values of the optical signals in response to the Stroop task stimuli could be measured (Plenger et al., 2016; Tam & Zouridakis 2014; Yamada et al., 2012). fNIRS data collection from the Boxy software was calibrated each time a subject donned the fNIRS headcap immediately before recording.

4.2.3 Optode Placement

The placement of the optodes for all fNIRS recordings is shown in Figure 4.1. The emitter and detector were between 2-4 cm apart. The larger the separation between them, the greater was the depth within the brain tissue from which signals were recorded. The emitters and the detectors were in a fixed cap so the relative distance between them was also fixed. The light from the emitters travels to the detectors and the equipment then records the infrared light signals, as modified by tissue oxygenation levels, and converts them to concentrations of oxy-Hb and deoxy-Hb. The fNIRS headcap was fastened to the subject's head with Velcro straps, using

the 10-20 International EEG system convention (Xiao et al, 2017). The first set of detectors, designated A and B (Figure 4.1) were placed on the “Nasion”. The optic channels from the emitters to the right of this set of detectors A and B was to be considered the right PFC (A and B even numbered channels, Figure 4.1). The channels from the left emitters to this detector were to designated as the left PFC (A and B odd numbered channels, Figure 4.1). The second set of detectors C and D was placed on the subject’s “Left Pre-Auricular Area” of the left hemisphere if they were right dominant, and vice-versa if left dominant. The dorsal channels (C and D odd-numbered) were considered to be monitoring the pre-motor area and the ventral channels (C and D even-numbered) were considered to be monitoring the motor area. In total, we had 4 detectors and 24 channels. The total amount of heat emitted by the infrared light was not too comfortable and experiments reached completion for most participants.

All subjects were instructed to minimize head movements. Lights in the recording room were turned off to prevent ambient light noise in the recordings (Scholkmann et al., 2014). The Stroop task stimuli was at the center of the computer screen and easily visible to the subject, so that the optical recordings were not compromised by the Stroop task measurements. If a subject had thick black hair, which would interfere with the absorption of the infrared light, recordings were made from only the prefrontal cortex (hair free forehead) but not from the motor cortex. Hair was removed from the optical fibers whenever possible and comfortable.

While the channel locations could be different with respect to the brain location from subject to subject, the relative changes after exercise or after rest for the general brain location did vary from subject-to-subject. Thus, the physiological interpretations of the data were consistent across all subjects.

4.2.4 Physiological Interpretation of Optical Signals

A schematic representation of how the fNIRS device records blood oxygenation levels as proxy for neural activity is presented in Figure 4.2. This schematic aids understanding of how to interpret an increase or decrease in the oxy-Hb or deoxy-Hb and the derived measures of total-Hb and diff-Hb. Oxygen in the blood diffuses to the neurons, interneurons and astrocytes as explained in 4.1.1 and 4.1.2, also depicted in Figure 4.2. The oxy-Hb concentrations will increase with higher amounts of oxygen delivered due to higher blood flow. If the brain tissue utilized the oxygen then the deoxy-Hb should increase. The oxygen extracted by the brain tissue can be estimated by the diff-Hb. When the total-Hb increases the oxygen-perfusion increases as the total availability of blood increase. Venous blood vessels could also constrict as a physiological by-product of exercising, and this would cause the release of oxygen from the deoxygenated blood back to the brain. Based on the literature review in Section 4.1, as a result of cerebral auto-regulation, the overall cerebral blood flow will remain the same after exercise even if the vascular pressure changes. The transient regional changes in the blood flow may be caused by constriction or dilation of blood vessels. After exercise, neuro-hormones like catecholamine could influence the flow of blood by reducing blood vessel diameters. These changes in the oxy-Hb, deoxy-Hb, total-Hb, diff-Hb are thus also referred to as “hemodynamic signals” (Plenger et al., 2016; Tam & Zouridakis, 2014).

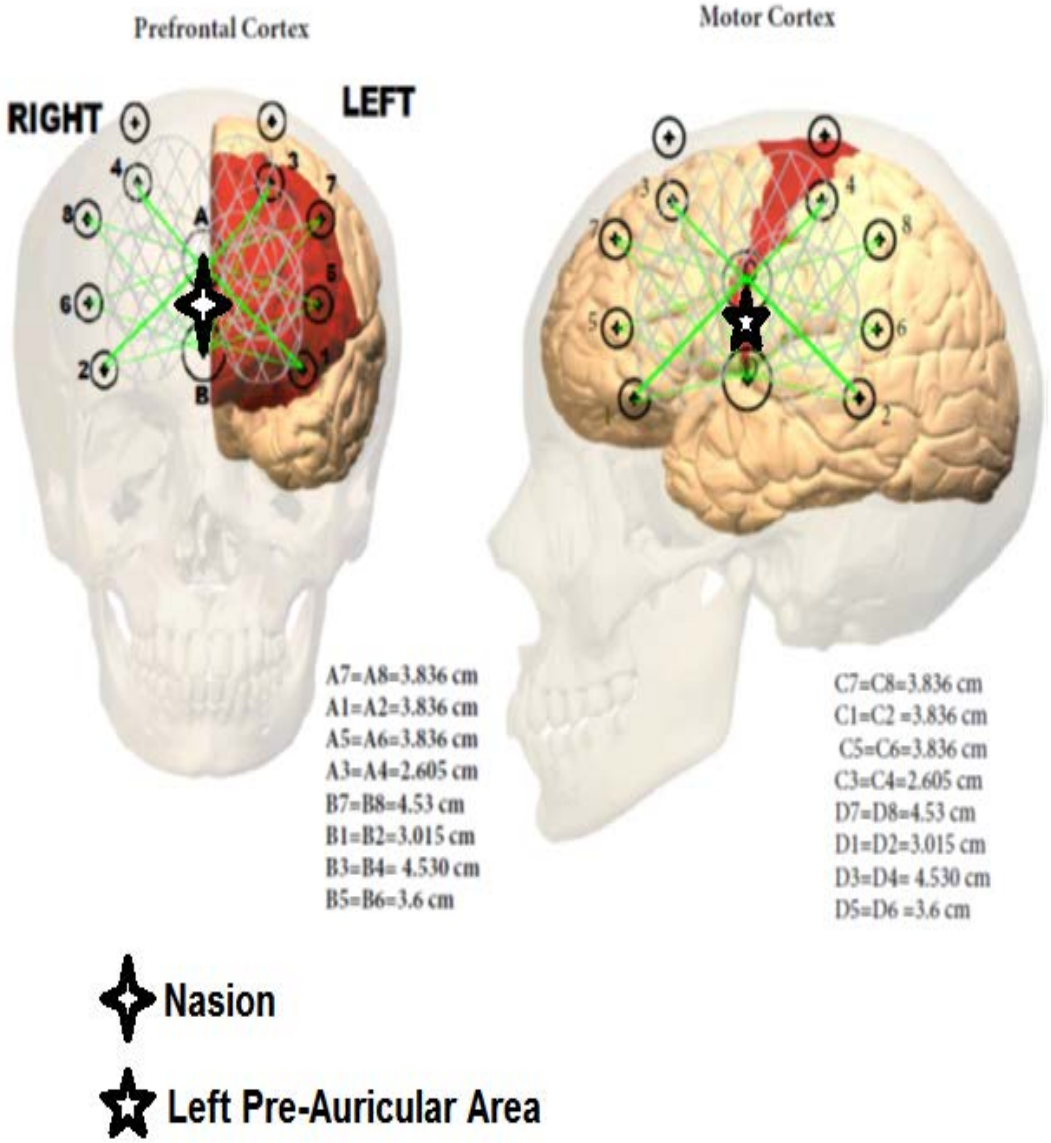


Figure 4.1. Placement of optodes at the prefrontal (left) and motor (right) cortices. ~ adapted from: Temporal Montage modified by Tam & Zouridakis; Original brain pictures by Anatomography [CC BY-SA 2.1 jp (http.//creativecommons.org/licenses/by-sa/2.1/jp/deed.en)], via Wikimedia Commons.

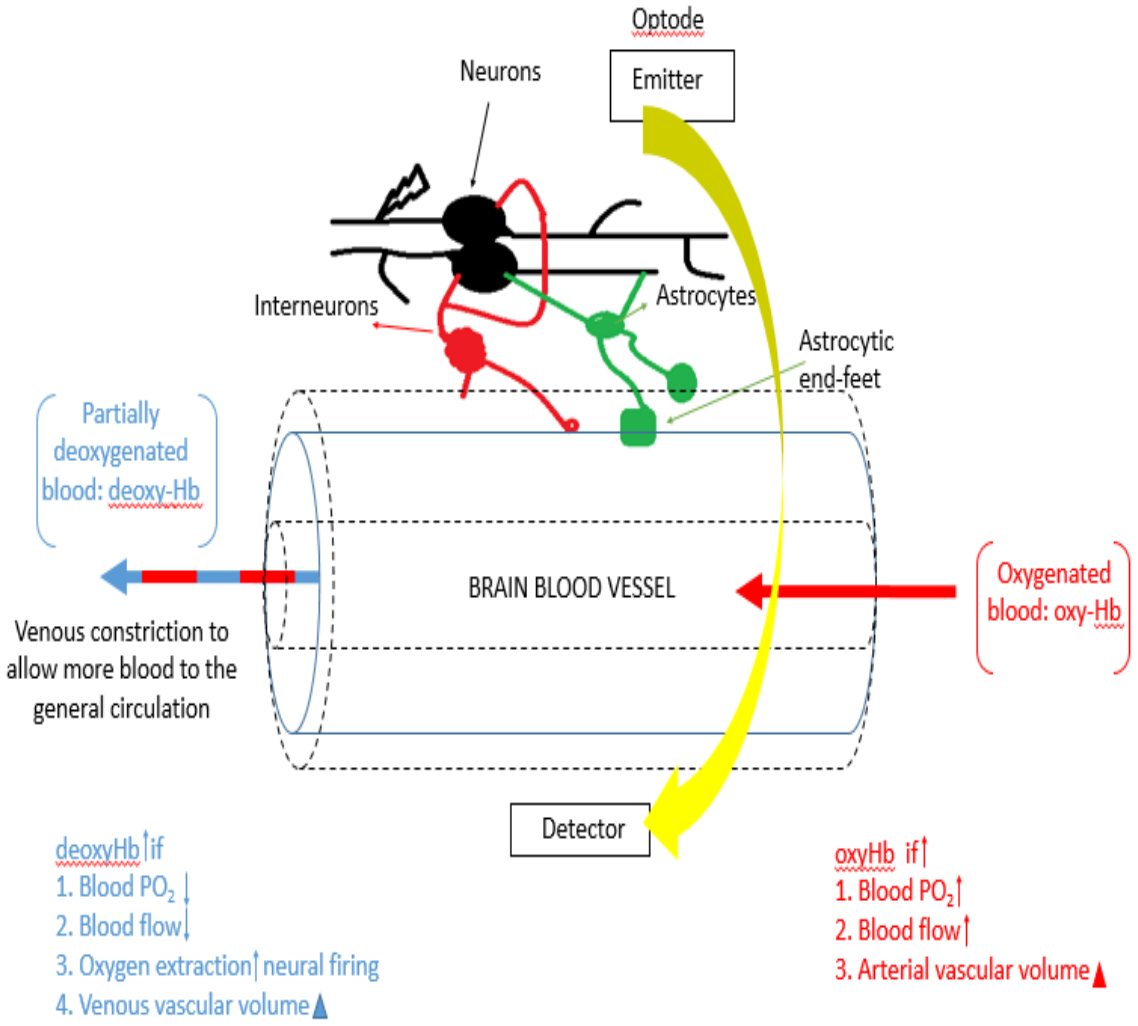


Figure 4.2. Schematic of optode placement relative to blood vessels and the flow through them.

4.2.5 Time Markers for fNIRS Recordings of Stroop Tasks

Time markers were recorded by the experimenter to synchronize with the onset and the end of the Stroop task for subsequent analyses (Figure 4.3). The neural recording consisted of a minimum of 5 seconds (secs.) and a maximum of 20 secs. of resting level baseline (subject instructed to sit stationary and not engage in any mental or physical task). This was followed by administration of the Stroop task, the length of which varied among the subjects. Typically, however, the length was about 40 secs for the incongruent Stroop task and about 20 secs. for the congruent Stroop task. This

was followed by another 5 secs. to 20 seconds (of resting- level post-task recording after the Stroop task. Since this was a time-averaged signal, both mean and standard error of the time-series points in the time-frame of interest were calculated. The relative changes in the calculations of the task or post-task hemodynamic signals were made from the baseline for the specific optode locations. Expanding upon Figure 2.1 and Figure 3.1, the specific details of the research design pertaining to the current chapter 4 is depicted in Figure 4.3. The data collected has been outlined at Table 4.1.

Table 4.1. Outline of brain hemodynamic data collected.

Brain Regions. I. PFC II. MC	For PFC. (n=12)	Channel#	For MC. (n=12)	Channel#
	Right (n=6) Left (n=6)	Right (A2, A4, A6, B2, B6, B8) Left (A1, A3, A5, B1, B5, B7)	For right handed individuals, the optode cap was tied on left MC; and vice versa	C1, C2, C3, C4, C5, C6 D1, D2, D5, D6, D7, D8
Brain Hemodynamic Signals.	I. Oxy-Hb II. Deoxy-Hb III. Total-Hb IV. Diff-Hb	Each signal had a Pre, Task, and Post as described in Figure 4.3 For statistical analyses across trials, or across subjects Task-Pre and Post-Pre signals were used		

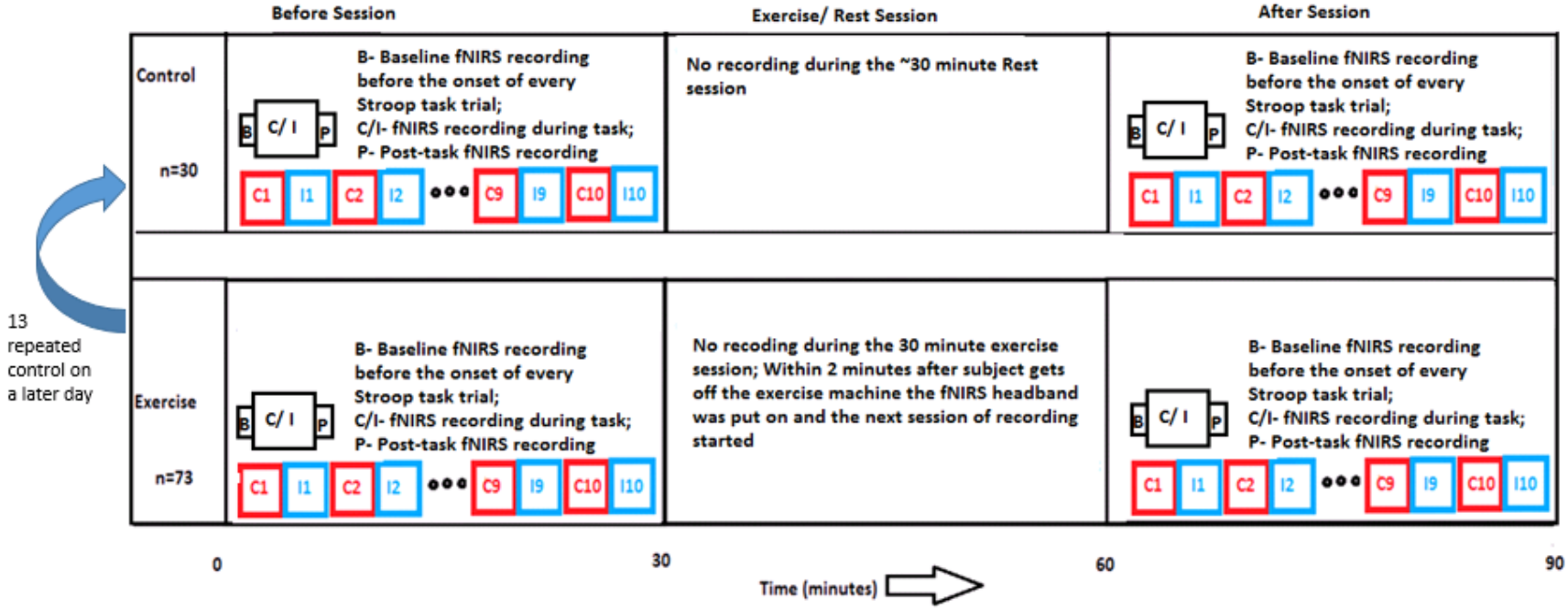


Figure 4.3. fNIRS recording during Stroop tasks. For each session (before and after), the fNIRS headcap was tied and the hemodynamic signals were recorded from the PFC and MC. Each trial recording consisted of right before (baseline, B), during (task, C/I) and right after (post-task, P) the Stroop task. Twenty such recordings were made consecutively with congruent and incongruent trials alternating in a pseudo-randomized style in each session (before/after). During the intermittent rest or exercise session, no fNIRS recording was performed.

4.2.6 Contemporary Data Analytical Techniques Used for fNIRS Stroop

Singh et al. (2015) adopted an fNIRS data-analysis procedure while subjects performed the Stroop task. The time average of the hemodynamic signals was done according to the task condition of pre-task baseline, during-task and post-task baseline. Block averaging was first used to signal average the time-series of hemodynamic signals (temporal averaging), corresponding to the different stimuli (baseline and task). This was carried out by taking the mean value during the plateau of the hemodynamic response when the hemodynamic response becomes stationery or stable (Butti et al., 2007). This approach can be used to determine the average hemodynamic response in response to a particular stimulus and peak time rather than peak amplitude has been correlated with neuronal activity modulations (Zaidi et al., 2015).

The general linearized model (GLM) is a common statistical tool used in fNIRS studies for investigation of the relationship between hemodynamic responses to the cortical activation and the corresponding predictor variables (Molteni et al., 2013; Imai et al., 2012; Butti et al., 2007). GLM is a goodness-of-fit multivariate statistical approach used to predict the response variable from one or more predictors. Usually, SPSS or SAS or even MS Excel is used for the GLM analysis. GLM theory can be applied to oxy-Hb and deoxy-Hb time series to provide reliable information on the subject's attentional state during the mental task (Butti et al., 2007). The hemodynamic change from the baseline is correlated with the cognitive activity state. Furthermore, additional predictors like exercise or meditation can be added to the existing GLM predictors of cognition (Singh et al., 2015).

4.3 Data Analysis Techniques

4.3.1 Single Subject Data Analysis

For confirming the outcome of the group analyses, single subject data analyses were conducted for ecological validation of empirical findings, a concept that determined the extent to which the conclusions of this research “exercise effects on cognition” was generalizable to whole populations. Ecological validation can be thought of as pooled together or meta-analysis of multiple case studies (Rosenthal & Rubin, 1986). This is an established approach in the Neurosciences (Brunswick, 1956; Parsons, 2015; Smith, 2012; Kazdin, 2010).

4.3.1.1 Signal Averaging to Remove Noise in Individual Trials in Each Subject

A time average of the hemodynamic signal in response to the Stroop task before the beginning of the stimulus (baseline), during the stimulus (task), after the stimulus ends (post-task) was performed to remove noise in the time series signals. The hemodynamic data was zero-corrected by subtracting the entire time series with the time averaged baseline value. Any significant changes in the time-averaged task values or post-task values from the baseline for each of the hemodynamic variables (oxy, deoxy, total, diff-Hb) at the 24 channels in the PFC and MC were noted.

4.3.1.2 Trial Averages and Effect Size Cohen’s D in Single Subjects

Cohen’s D is an effect size measure to indicate the standardized differences between two means (Lakens, 2013; Fritz et al., 2012; Becker, 2000; Cohen, 1988). To determine whether there were task-related changes in the 10 trials in one subject for the specific conditions of congruent and incongruent tasks, both before and after exercise, the effect sizes for each trial were calculated as:

Equation 3:

$$\text{Cohen's d trial 1, } D\_t1 = \frac{(M1\_task - M1\_pre)}{SD\_pre}$$

where, M1_post = time averaged hemodynamic signal during Stroop task trial 1,

M1_pre= time averaged hemodynamic signal during baseline trial 1,

SD_pre= standard deviation pooled for all the 10 trials

For all 10 trials in one subject, the above values were averaged to determine the Cohen's D for a specific condition, calculated as (D_t1 + + D_t10) / 10.

4.3.1.3 Phase Plots in Single Subject

Linear phase plots were a type of time-series signal processing filter, used to correlate the relationship of two time-series, which helped determine any hysteresis effects (lag) from the slope of the correlation (Collett et al., 2014; Esser et al., 2013; Oprisan et al., 2013). In this case, the time-series hemodynamic signals of oxy-Hb vs. deoxy-Hb were plotted to determine if they were phase-coupled (negatively or positively correlated) or out of phase (uncorrelated and elliptical nature of correlation) for each of the brain regions corresponding to the Stroop task stimuli. In general, one expects to see an in-phase response for the oxy vs. deoxy-Hb conditions when the oxygen supply meets the demand. The out of phase oxy-Hb vs. deoxy-Hb situation could occur when the supply of oxygen does not match the demand. If the oxy-Hb and deoxy-Hb were negatively or positively correlated, then in either situation they were coupled. If the oxygen delivery was more than extraction, then that can be estimated by the steepness of the trend-line of the cluster between oxy-Hb and deoxy-Hb. The steeper the curve fits, the greater is oxygen demand for the supply. The trend-lines

were expected to change for the before vs. after exercise conditions.

4.3.1.4 Spearman's Rho Correlations of Brain-Behavioral Data in Single Subject

Behavioral and brain-hemodynamics data were correlated with Spearman's Ranked correlations, as the behavioral data showed non-normal distribution (Table 2.3, Table 2.4). In addition, the units of the reaction time or number of errors and hemodynamic signals were in different scales and a standardized no-unit correlation was possible using non-parametric Spearman's Rho (Liu et al., 2016; Mukaka, 2012). Each of the hemodynamic variables were correlated to the 24 channels in the Prefrontal and Motor Cortices to the reaction time and accuracy data for each subject for the 10 trials. Later the trend was assessed for similarity between subjects.

Non-parametric Spearman's ranked correlation was used to correlate the Spearman's ranked accuracy or reaction time data with the Spearman's ranked trial-averaged (task-baseline) hemodynamic data in each subject for the 10 trials in each of the following conditions: congruent before exercise, congruent after exercise, incongruent before exercise and incongruent after exercise. When correlation was found for a certain hemodynamic variable, then that variable was implicated as a component of executive function. This allowed evaluation of whether the right versus the left prefrontal cortex locations showed similar or opposite correlation effects. A similar analysis was performed for the motor cortex. This allowed comparisons of the correlations before and after exercise. The same procedure was repeated for the rest experiments so that in future exercise-specific effects could be teased apart from practice effects.

4.3.2 Group Data Analysis

In order to remove noise and to get a consistent pattern in the data, which reflects the evoked changes in response to the Stroop tasks, we needed to do the group data analysis. We started with the summary or grouping of the two outcome measures- Cohen's D and Spearman's Ranked correlations (Rho) in all the subjects. This is a common practice in epidemiological (health) related studies (Velentgas et al., 2013).

4.3.2.1 RM-ANCOVA Before and After Exercise

We used RM-ANCOVA to compare the before and after exercise sessions to determine exercise specific changes in the trial averaged hemodynamic responses. Repeated-measures ANCOVA was performed because the same subject was recorded multiple times. The dependent variables were the trial-averaged concentration changes of oxygenated (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb), and derived variables of total hemoglobin change (total-Hb) and difference hemoglobin change (diff-Hb). A *post hoc* LSD (Least Square Differences) adjustment was performed for multiple comparisons between the before and after exercise sessions. The "within subject" factors were congruent and incongruent tasks. The next "within subject" factors were the 24 channels or brain locations which tested the prefrontal cortex from motor cortex location and also right from left PFC being analyzed to test for the lateral neural activation patterns since right PFC has previously been implicated in decision making (Ye et al. 2015). The next "within subject" factor was the time marker, delta task (task-baseline) and delta post (post-task – baseline) values similar to Singh et al. (2015). Change in HR was the covariate in this RM-ANCOVA model as we know HR changes immediately after exercise (Carey et al,

2005). Change in HR was indicative of whether the subject exercised at the target 70% of maximal HR and we know from section 3.6.2 that the HR did vary by 67% between before and after exercise sessions. Repeated measures, a parametric test, was used since the hemodynamic signals were so small in value and had several repeated measures (large n) over multiple channels and time points, etc. and were thus considered normally distributed, as a standard practice (Plenger et al., 2016; Singh et al, 2015). In summary, the RM-ANCOVA model had the following conditions:

- All subjects who completed exercise, n=73
- Trial-averaged hemodynamic data from the congruent and incongruent Stroop tasks as dependent variables in two separate RM-ANCOVA (since the two Stroop tasks were testing two separate cognitive tasks)
- Change in HR as a co-variate as change in HR
- Repeated factors or independent variables:
    - Exercise - two levels: before and after
    - Hemodynamics ‘Hb’- four levels: oxy-Hb, deoxy-Hb, total-Hb, diff-Hb
    - Time - two levels: during delta task, delta post
    - Channels - 24 levels

4.3.2.2 Cohen’s D Group Data Tally

Meta-analysis of effect size Cohen’s D measures is well-established (Rosenthal & Rubin, 1986; Fritz, 2011; Lakens, 2013). All the conditions in all the subjects were screened to find the subjects that were most consistent in the 10 trial responses from the baselines. The objective criterion for inclusion/exclusion was a Cohen’s D value of>0.8 or <-0.8 for each channel or brain region in response to the particular congruent or incongruent Stroop task before or after exercise. Cohen’s D reflected the task responsive channels in each subject or in other words which channels showed a consistent increase or decrease during task or during post-task from the baseline in

each subject. Congruent, incongruent, before or after sessions for exercise and rest controls were all analyzed separately and was later pooled together for categorical analysis. This was followed by a group summary for all the subjects reflecting the best task responsiveness in all channels in all subjects. This was achieved by counting the number of subjects that showed the highest Cohen's D the maximum number of times. The channels that showed the highest Cohen's D for the majority of the subjects in this tally were attributed to be the most task responsive channels—that is, whether the PFC or the MC were most Stroop task responsive, and whether the oxy-Hb (systemic), deoxy-Hb (neuronal), total-Hb (systemic), diff-Hb (neuronal) were most Stroop task responsive. However, the limitation of this technique is we do not have a direct correlation to the behavioral data, and we do not know if the task responsiveness was specifically correlated to the RT or mistakes in the Stroop tasks. Thus, in addition, we needed to create a tally or summary of the Rho outcome measure that correlated the hemodynamic with the behavioral data.

4.3.2.3 Rho Group Data Tally

For each of the before and after sessions of exercise and rest, and for congruent and incongruent Stroop tasks we created the summary of the best Rho measures in all subjects. The Rho measures considered were the best-correlated Rho measures of the hemodynamic and RT, and the best-correlated Rho measures of the hemodynamic and mistakes values in each of the subjects. MS Excel 'mode', 'index' functions were used to pool the most frequent channels that were showing the highest Rho values in the majority of the subjects. Additionally, the channels were also categorized as left or right PFC, and pre-motor and primary-motor cortices and were then re-analyzed using the same technique. The majority percentages in all the

subjects were noted. The reason, why we also pooled the data not just with the specific channel names, but also with the channel locations (right- or left- PFC, or pre- or primary- MC) was to accommodate the fact that exact location of the channels will vary (refer to section 4.2.3). Eventually, we were able to locate the regions in the brain most correlated to each of the behavioral measures of RT and mistakes rate in each of the Stroop tasks in each of the before or after exercise or rest conditions. We also created the averages of the Rho values for the most correlated channels by using 'average' and 'mode' functions in MS Excel. This was done so that we could later compare the differences (significant or not) between the before and after sessions (paired samples) and between the exercise and rest conditions (independent samples).

4.4 Results

4.4.1 Data Analysis Format Demonstrated in Single Subject

This section focuses upon data from a single individual to illustrate the form of the raw data collected in this study.

4.4.1.1 Raw Hemodynamic Data

Raw data changes in the brain hemodynamic data recorded at channel B2 in one subject during multiple trials and during multiple conditions are shown in Figure 4.4. This subject showed stationery baselines in the hemodynamic signals. For the incongruent trials, the oxygen delivery (oxy-Hb) showed a decreasing trend compared to baseline, during incongruent trials and congruent trials before exercise. After exercise, oxygen delivery (oxy-Hb) and oxygen extraction (indicated by deoxy-Hb) ed compared to baseline. The derived variables of cerebral blood volume (total-Hb) and cerebral oxygenation (diff-Hb) co-varied with the oxy-Hb. The deoxy-Hb changed the

least amongst the four hemodynamic variables. The raw data presented in Figure 4.4 also indicated that the channel B2 was task-relevant for Stroop tasks, as deduced from the fact that there were noticeable task-related changes in the hemodynamics compared to the baseline.

4.4.1.2 Raw Data: Time Averaged

Trial-averaged brain hemodynamic signals for 10 trials for the incongruent Stroop Task recorded from the channel B2 from the same subject presented above are presented in Figure 4.5. The oxy-Hb and deoxy-Hb hemodynamic responses in Figure 4.5 were the opposite of each other, as predicted. After exercise, total-Hb response increased compared to before exercise, indicating perfusion with oxygenated blood in the recorded neurons has increased after exercise.

4.4.1.3 Raw Data: Effect Size Cohen's D for 10 Trials

Again, for initial illustrative purposes and to provide evidence for later group data analysis outcome, the effect sizes 'Cohen's D' measures were compared for before and after exercise sessions in a single individual. Figure 4.6 shows the data from the same subject at channel B2. Highly negative Cohen's D values before exercise indicate consistent decreases in cortical oxygenation signal (both task and post) from the baseline in the 10 trials. After exercise, consistency was low, but there were increases from the baseline. This confirmed statistically the trends seen in the trial averages results in Figure 4.5.

4.4.1.4 Correlations of Behavioral Data with Hemodynamics in single subject (Rho)

To compare the changes in Spearman's ranked (Rho) correlation of brain

hemodynamics immediately after exercise, we first calculated the Rho for 10 trials in each subject. We correlated the Spearman's ranked measures of RT or number of error of congruent or incongruent Stroop tasks with oxy-Hb, deoxy-Hb, total-Hb and diff-Hb in each of the 24 channels, for the before and after exercise or rest sessions.

4.4.1.4.1 Example, Rho between Incongruent Accuracy α PFC Hemodynamics

Brain hemodynamic data were correlated with the number of errors incurred in performing Stroop tests. The slopes of these correlations were compared before and after exercise. Channel A4 showed significant correlations (p<0.1, n=10) in the incongruent Stroop task after exercise compared to before exercise in a single subject (Figure 4.7 A). Deoxy-Hb in that subject was highly negatively correlated with incongruent mistakes rate immediately after exercise when there was no correlation before exercise.

4.4.1.4.2 Trial Averaged deoxy-Hb Comparison Before and After Exercise with Number of Errors

The number of errors in the incongruent task for the same subject were assessed before and after exercise. Before exercise, the subject made 11 errors and after exercise, she made five errors. Comparably, the ten trial-averaged deoxy-Hb values at channel A4 showed deactivation during the incongruent Stroop task before exercise and activation after exercise (Figure 4.7 B & C). This implied higher oxygen extraction at this brain region after exercise, helping the the subject cope by making fewer mistakes in the incongruent Stroop task. This subject had 15% faster RT and 17% increase in HR after exercise.

4.4.1.4.3 Phase Plots of the Time-Series Deoxy-Hb vs Oxy-Hb Data

The hysteresis effect was estimated by plotting all the deoxy-Hb time series values for the 10 trials against the oxy-Hb values to verify if there was a time lag in the deoxy-Hb response compared to the oxy-Hb response and if exercise impacts this oxy-Hb - deoxy-Hb coupling (Figure 4.7 D & E). Deoxy-Hb lagged behind oxy-Hb response and the two were negatively coupled. The phase plot between the time-series responses of deoxy-Hb and oxy-Hb for the after-exercise condition (Figure 4.7 E) showed better coupling (steeper slope) compared to the before-exercise condition (Figure 4.7 D). For both the before- and after-exercise conditions, the deoxy-Hb laged behind oxy-Hb, which meant the metabolic response of deoxy-Hb came after the oxy-Hb response. This explained why in the raw data (Figure 4.4) the oxy-Hb values fluctuated more than the deoxy-Hb. Essentially, the deoxy-Hb response took longer to change as this metabolic response had a lag. Moreover, the after-exercise phase plot was steeper than the before exercise (Figure 4.7 D & E), meaning that the oxygen demand (deoxy-Hb) was not met by the oxygen delivered (oxy-Hb) after exercise. This finding also points to the greater activation of neurons in this region after exercise. This could explain how exercise may improve executive function (in incongruent Stroop task involving conflict-resolution) due to higher activation of neurons in the right PFC.

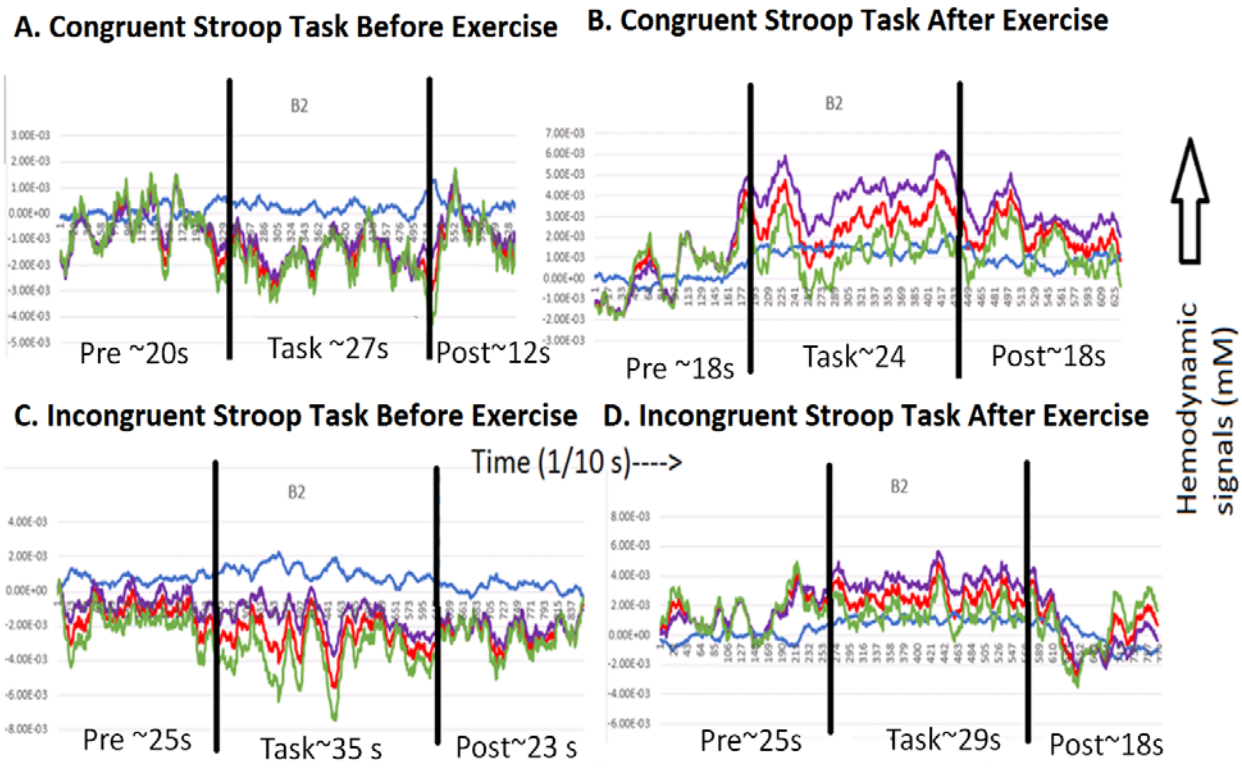


Figure 4.4. Raw hemodynamic data. The four hemodynamic variables are plotted on the y-axis, and the x-axis represented time in units of 100 msec. or 1/10 of sec. The first time-marker (dotted blue line) denotes the onset of the stimulus (i.e., the start of Stroop task). The second time-marker denotes the end of Stroop task. Prior to the first time-marker comprises the baseline period, from first to second time marker time denotes the period of the task, and from second time-marker to end of the trial comprised the post-task. Panels A and B denoted brain hemodynamic responses to congruent Stroop task before and after exercise, respectively, whereas Panels C and D represented the incongruent Stroop task before and after exercise. Recordings were in the same subject at channel B2.

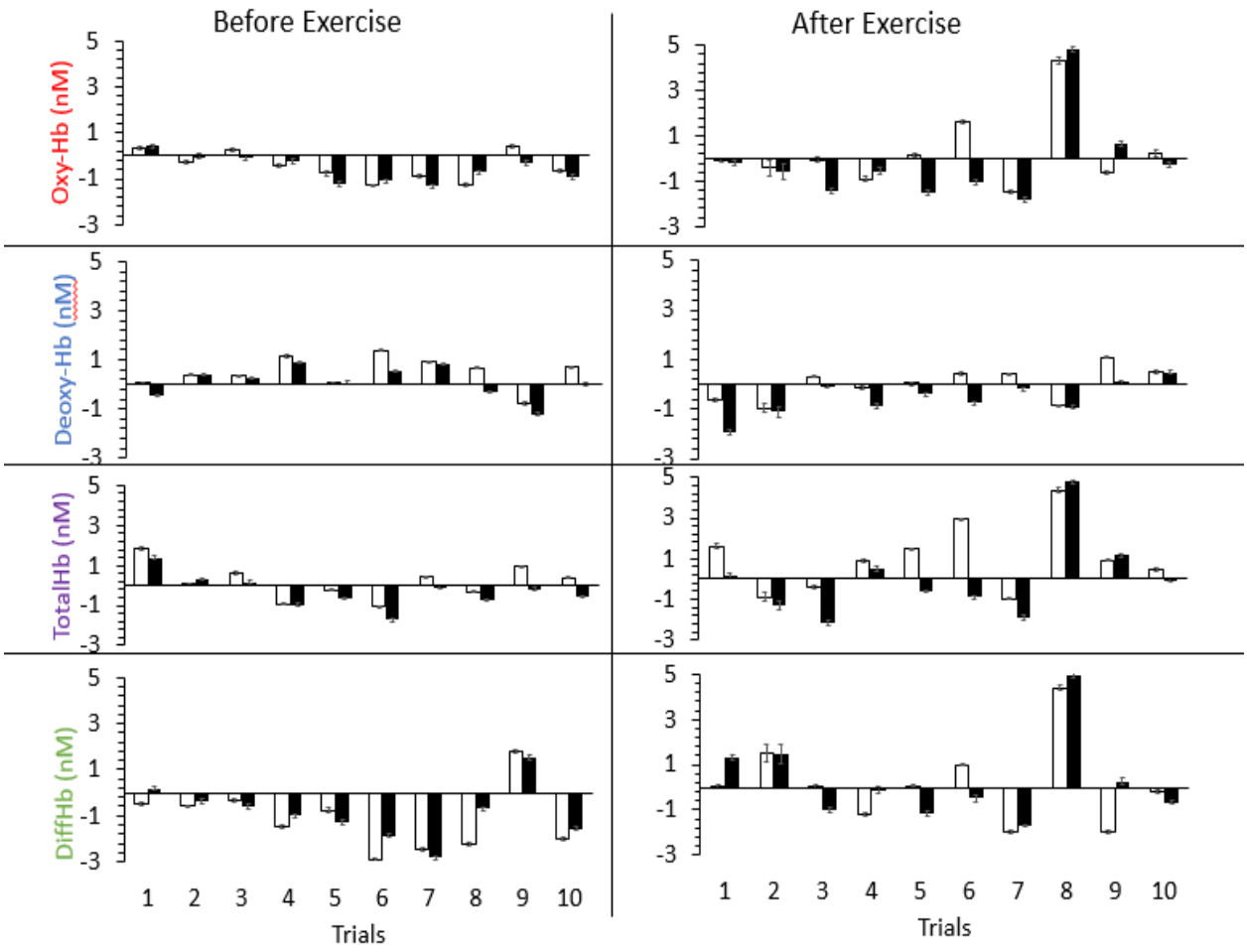


Figure 4.5. Trial averaged brain hemodynamic signals before (A) and after (B) exercise. Time-averaged delta Task (white) and delta Post (black) signals () for each of the 10 trials in same subject for incongruent Stroop task at channel B2. Means±Standard Error bars are presented.

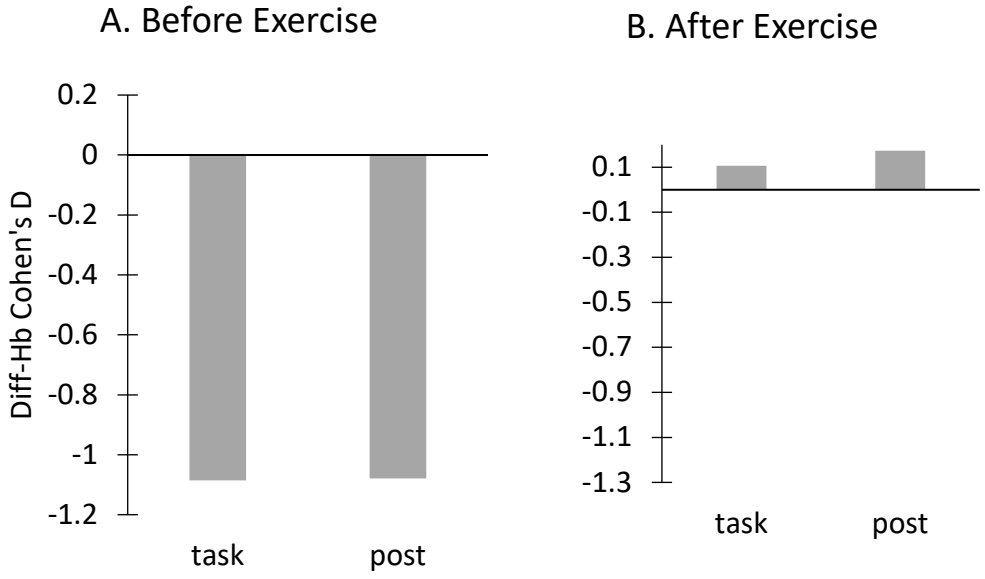


Figure 4.6. Cohen's D (individual) A. before exercise and B. after exercise.

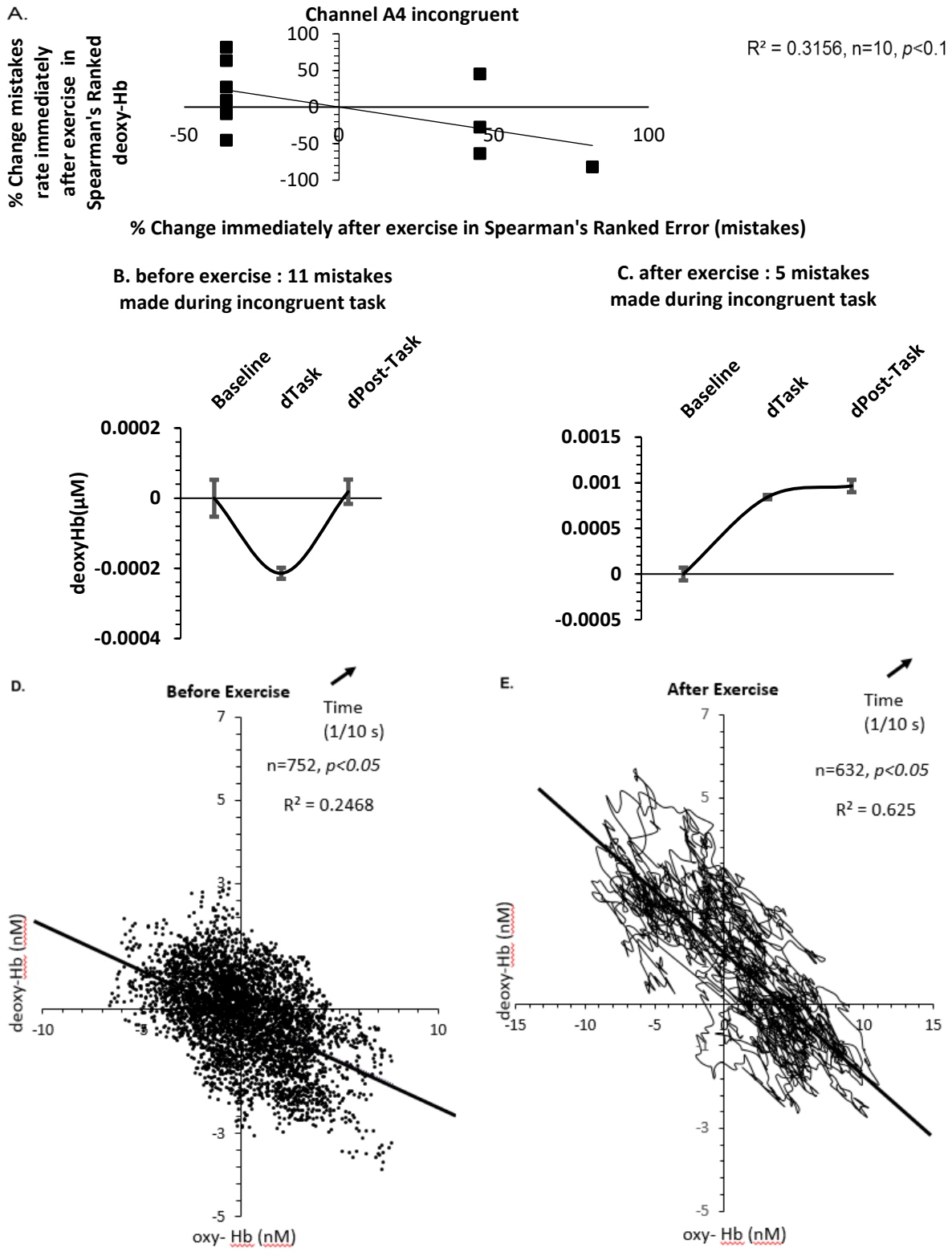


Figure 4.7. Hemodynamics and mistakes correlation. (A) Change in Mistakes (incongruent) Rho correlation with deoxy-Hb after exercise at right PFC channel A4 (individual subject). (B) & (C) Comparison of trial averaged deoxy-Hb with number of errors for same subject before and after exercise. (D) & (E) Phase plot of time series ∆ deoxy-Hb vs ∆oxy-Hb at channel A4 for incongruent task before and after exercise in the same subject.

4.4.2 Group Data Analysis Results

Having shown the format for the raw data and analysis within an individual, we now turn to analysis of the group data.

4.4.2.1 Comparisons of Trial Averages Before and After Exercise Sessions

RM-ANCOVA model (section 4.3.2.1.) was conducted on the trial-averaged hemodynamic data before and after exercise in 73 subjects. The most significant main effect of exercise on the hemodynamic data at the specified channels as represented by Figure 4.8. The hemodynamic changes after exercise during both the congruent and incongruent Stroop tasks were at PFC channels (bilateral- opposite hemodynamic responses for left and right PFC). Moreover, the hemodynamic changes for the congruent and incongruent Stroop tasks were neuronal (deoxy-Hb and diff-Hb).

4.4.2.2 Task Responsiveness

The method of this analysis has been outlined in section 4.3.2.2.

4.4.2.2.1 Rest Controls

In the rest experiments, Table 4.2 represents the tally of number of subjects showing high Cohen' D effect sizes out of 30 subjects examined. Hemodynamic responses to the Stroop tasks were observed from the same channels as in the exercise experiments. We also obtained a similar outcome as following exercise in section 4.4.2.2 with Channels A6, B2, A5, and B1 at the prefrontal cortex, with these signals being the most task-responsive for the highest number of subjects (shadowed cells in Table 4.2). In addition, deoxy-Hb was not in the list because it rarely changed from baseline, similar to what was observed with the exercise experiments.

4.4.2.2.2 Exercise Experiment

The meta–analysis on Cohen's D values indicating task responsiveness is shown in the tally in Table 4.3. This table depicts the number of subjects who had high effect size 'Cohen's D' changes in the incongruent task responses from baseline. The hemodynamic data collected during the incongruent Stroop task were consistently different from baseline during the 10 trials as shown by the high effect size Cohen's D values. The number of subjects that show the high effect sizes (Cohen's D>0.8 or <-0.8) in terms of task-related hemodynamic responses (task different from baseline, or post-task different from baseline) came from the channels indicated in Table 4.3 out of all possible 24 channels, either before or after exercise conditions. Moreover, for the same channel, there were individual differences in that some subjects showed high effect size increases and others showed high effect size decreases in Cohen's D values. Of the blood oxygenation signals, deoxy-Hb showed the least changes and did not top the tally list. Compared to other channels, B1, A5 (left PFC) and B2, A6 (corresponding right PFC) channels showed consistent changes right after the Stroop tasks (post) compared to baseline, as indicated by high effect size Cohen's D values. It was interesting that motor cortex channels did not show the highest number of subjects with high Cohen's D effect sizes for task responsiveness. This meant that PFC was more Stroop task-responsive than MC.

4.4.2.3 Group Data- Comparing Rho Before and After Exercise

Spearman's Rho for each subject correlating brain and behavioral data were pooled together and compared for the before- and after- rest and exercise conditions to determine how they change. The method for this analysis has been outlined in

section 4.3.2.3. The results for the rest controls and exercise experiments are displayed in Table 4.4 and Table 4.5 respectively.

Left PFC and pre-MC were consistently correlated to both the RTs of congruent and incongruent Stroop tasks for before and after rest control sessions (Table 4.4). Around 15-40% of the total sample (30) in the rest sessions displayed this pattern. Right PFC and motor cortex (insula) were correlated to mistakes in the incongruent Stroop task (Table 4.4). Around 30% of the rest sample population showed the pattern with the novel exposure to the incongruent Stroop task. In the after session, which is with habituation, the percentage of subjects that correlated to the same brain regions of right PFC and motor cortex (insula) dropped to about 15% (Table 4.4). Lesser percentage of subjects (10%) showed correlation of the mistakes made in the congruent Stroop tasks to the hemodynamics, and the right PFC and primary MC were active when mistakes were made in the congruent Stroop task. For incongruent Stroop task the hemodynamic changes correlated with the behavioral data were neuronal (deoxy-Hb and diff-Hb) for both the before and after sessions, yet for the congruent Stroop task the hemodynamic changes were both systemic (total-Hb) and neuronal (diff-Hb and deoxy-Hb) (Table 4.4).

After exercise, the hemodynamic changes correlated with the congruent RT were more at the MC rather than at the PFC (Table 4.5). After exercise, fewer by 32 % of the total number of subjects (73) correlated less to the pre-MC with the incongruent Stroop task RT (Table 4.5). The hemodynamic changes were systemic (total-Hb) before exercise and neuronal (deoxy-Hb) after exercise for the small percentage of the population whose incongruent Stroop task RT, which correlated with the pre-MC hemodynamics. Left PFC correlated best with mistakes, both congruent and incongruent Stroop tasks both before and after exercise, however, the

hemodynamic changes correlated with mistakes after exercise were more systemic (oxy-Hb) changes (Table 4.5).

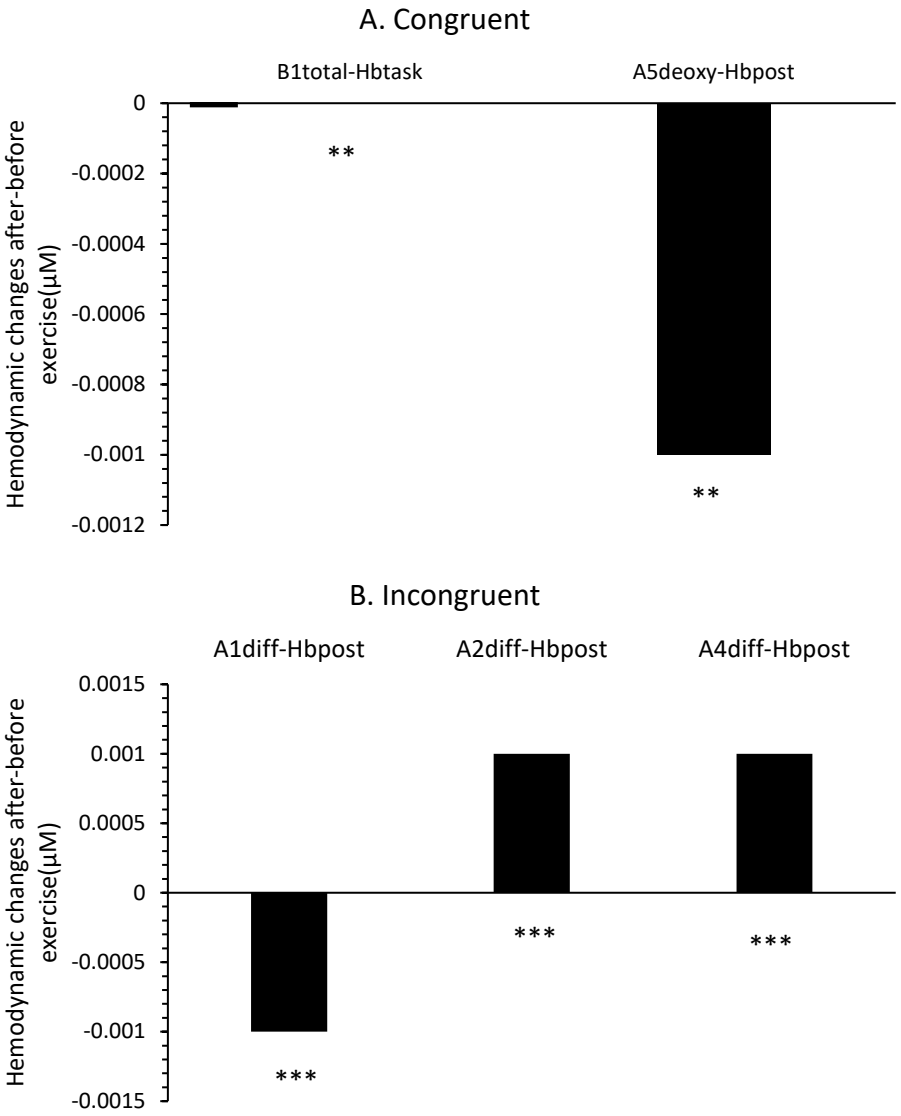


Figure 4.8. After-Before exercise changes in trial-averaged hemodynamic data. (A) Immediately after exercise most significant changes (**, p<0.01, n=73) in the trial averaged hemodynamics at channel B1 and A5 (location in left PFC) for congruent Stroop task. (B) Immediately after exercise most significant changes (***, p<0.001, n=73) in the trial averaged hemodynamics at channel A1 (location in left PFC) and channels A2 and A4 (location in right PFC) for incongruent Stroop task.

Table 4.2. Cohen's D values task responsiveness for rest experiment. The channels corresponding to the colored cells showed highest number of individuals out of n=30, who showed high effect size Cohen's D values. These subjects showed consistent changes in the task values compared to the baseline in all the 10 trials per condition.

Rest Conditions	high '+D'	high '-D'	high '+D'	high '-D'
	before rest		after rest	
oxyHb-congruent-deltapost-A6	8	5	5	7
oxyHb-incongruent-deltapost-A6	3	8	4	9
totalHb-incongruent-deltapost-A6	2	10	2	8
oxyHb-incongruent-deltatask-B2	4	8	6	7
oxyHb-congruent-deltapost-A5	3	4	9	1
oxyHb-incongruent-deltapost-B2	6	5	5	8
oxyHb-incongruent-deltatask-A6	3	7	3	8
totalHb-incongruent-deltapost-B2	3	6	5	8
oxyHb-incongruent-deltapost-B1	3	4	4	8

Table 4.3. Cohen's D values task responsiveness for exercise experiment. The channels corresponding to the colored cells showed highest number of individuals out of a total of 73 individuals, who showed high effect size Cohen's D values. , In other words, these subjects showed consistent changes in the task values compared to the baseline in all the 10 trials per condition. Refer to section 4.3.3 for explanation on how the Cohen' D measures were obtained.

Exercise Conditions	high '+D'	high '-D'	high '+D'	high '-D'
	before exercise		after exercise	
oxyHb-congruent-deltapost-A6	6	5	7	3
totalHb-congruent-deltapost-A6	4	5	7	5
oxyHb-congruent-deltapost-B1	2	4	8	4
oxyHb-incongruent-deltapost-A5	7	4	3	8
oxyHb-incongruent-deltapost-A6	8	6	5	7
oxyHb-incongruent-deltapost-B1	12	2	4	8
oxyHb-incongruent-deltapost-B2	8	6	4	11
oxyHb-incongruent-deltapost-A3	5	2	5	7
diffHb-incongruent-deltapost-A6	8	6	3	5
totalHb-incongruent-deltapost-B1	7	0	5	5
diffHb-incongruent-deltatask-B2	7	3	1	4
diffHb-incongruent-deltapost-B2	7	7	2	5

Table 4.4. Rho summary data for rest control. Condition represents the behavioral data to which the hemodynamics was correlated positively (+) or negatively (-). n represents the number of subjects that represents the majority of subjects showing high correlation values of the behavioral condition with the hemodynamic state at the stated brain region. Task represents the hemodynamic changes during the Stroop task and post represents the hemodynamic changes right after the completion of the Stroop tasks. The lighter shaded average rho values represents statistically significant positive correlations, $p<0.05$ and the darker shaded average rho values represents statistically significant negative correlations, $p<0.05$. Italicized hemodynamics represents the brain regions consistently correlated the same way to cognition both before and after rest controls (meaning repeated measures showing consistency in terms of response correlation to the brain regions). In the rest group (total n=30), between 3-43% of the total population showed highest consistency in the correlation of the behavioral response of the Stroop tasks to the noted brain regions. Underlined text represents the systemic or neuronal hemodynamic measures that correlate to the cognitive behavioral data in the consistently active brain regions.

		Before Rest Control				After Rest Control			
Correlation	Condition	Hemodynamics	n	% out of 30	average Rho	Hemodynamics	n	% out of 30	average Rho
+	congruent RT	LeftPFCdifftask	4	13.33	0.86	Pre-MCdeoxytask	12	40.00	1.11
-		PrimaryMCoxytask	3	10.00	-0.61	Pre-MCdifftask	7	23.33	-0.47
+		LeftPFCoxypost	2	6.67	0.77	Pre-MCdeoxypost	4	13.33	0.86
-		*LeftPFC* diffpost	4	13.33	-0.57	*LeftPFC* totalpost	6	20.00	-0.53
+	incongruent RT	Pre-MCdeoxytask	8	26.67	0.99	LeftPFCoxytask	1	3.33	0.78
-		*LeftPFC* deoxytask	6	20.00	-0.52	*LeftPFC* deoxytask	13	43.33	-0.32
+		Pre-MCoxypost	3	10.00	0.80	PrimaryMCdeoxypost	4	13.33	0.84
-		Pre-MCdiffpost	2	6.67	-0.66	LeftPFCdeoxypost	2	6.67	-0.66
+	congruent mistakes	Pre-MCoxytask	2	6.67	0.74	LeftPFCdeoxytask	2	6.67	0.76
-		Pre-MCdifftask	1	3.33	-0.69	LeftPFCdeoxytask	3	10.00	-0.60
+		*RightPFC* totalpost	2	6.67	0.76	*RightPFC* deoxypost	3	10.00	0.78
-		*PrimaryMC* diffpost	1	3.33	-0.64	*PrimaryMC* deoxypost	2	6.67	-0.65
+	incongruent mistakes	*RightPFC* deoxytask	11	36.67	1.05	RightPFCdeoxytask	5	16.67	0.88
-		*Pre-MC* oxytask	6	20.00	-0.53	*Pre-MC* deoxytask	4	13.33	-0.60
+		LeftPFCdiffpost	1	3.33	0.73	RightPFCdiffpost	6	20.00	0.91
-		PrimaryMCdiffpost	4	13.33	-0.61	RightPFCdeoxypost	3	10.00	-0.59

Table 4.5. Rho summary data for exercise experiment. Refer to Table 4.4, for the naming convention. Italicized hemodynamics represents the brain regions consistently correlated in some way to cognition both before and after exercise (meaning repeated measures showing consistency in terms of response correlation to the brain regions). In the exercise group (total n=73), between 1-29% of the total population showed highest consistency in the correlation of the behavioral response of the Stroop tasks to the noted brain regions. Left PFC was most correlated to mistakes; pre-MC was most correlated to the incongruent RT in the Stroop tasks even after exercise.

		Before Exercise Experiment				After Exercise Experiment			
Correlation	Condition	Hemodynamics	n	% out of 73	average Rho	Hemodynamics	n	% out of 73	average Rho
+	congruent RT	LeftPFCtotaltask	7	9.59	0.83	Primary-MCoxytask	5	6.85	0.81
-		RightPFCdeoxytask	1	1.37	-0.69	LeftPFCoxytask	5	6.85	-0.65
+		RightPFCoxypost	11	15.07	0.90	Pre-MCdeoxypost	2	2.74	0.76
-		*LeftPFCdeoxypost*	*3*	*4.11*	*-0.68*	*Pre-MCdeoxypost*	*11*	*15.07*	*-0.59*
+	incongruent RT	Pre-MCdifftask	3	4.11	0.78	Primary-MCtotaltask	3	4.11	0.77
-		*Pre-MCtotaltask*	*25*	*34.25*	*-0.39*	*Pre-MCdeoxytask*	*1*	*1.37*	*-0.69*
+		RightPFCdiffpost	1	1.37	0.74	RightPFCdeoxypost	2	2.74	0.77
-		*Pre-MCoxypost*	*2*	*2.74*	*-0.71*	*Primary-MCdiffpost*	*1*	*1.37*	*-0.72*
+	congruent mistakes	Pre-MCdifftask	4	5.48	0.73	Primary-MCdeoxytask	8	10.96	0.78
-		*LeftPFCoxytask*	*15*	*20.55*	*-0.48*	*LeftPFCdeoxytask*	*4*	*5.48*	*-0.61*
+		LeftPFCoxypost	1	1.37	0.69	LeftPFCoxypost	3	4.11	0.72
-		*LeftPFCoxypost*	*1*	*1.37*	*-0.66*	*LeftPFCoxypost*	*21*	*28.77*	*-0.39*
+	incongruent mistakes	LeftPFCoxytask	21	28.77	0.96	RightPFCoxytask	6	8.22	0.75
-		RightPFCdifftask	4	5.48	-0.65	LeftPFCoxytask	2	2.74	-0.64
+		RightPFCoxypost	4	5.48	0.74	LeftPFCoxypost	3	4.11	0.72
-		*LeftPFCoxypost*	*20*	*27.40*	*-0.41*	*LeftPFCoxypost*	*4*	*5.48*	*-0.60*

4.5 Discussion

The switch from mitochondrial to glycolytic machinery for neuronal firing (Jang et al., 2016) could explain the lag in the metabolic response for the deoxy-Hb compared to the oxy-Hb. When enough oxygen is being delivered (oxy-Hb) to brain tissue, the neurons utilized mitochondrial oxidative phosphorylation. Soon after, the energy mode shifted to being glycolytic as oxygen delivery was no more sufficient for pertinent functional processing in the brain. The oxygen extraction variable (deoxy-Hb) variable then started changing. Thus, oxy-Hb changed rapidly, but deoxy-Hb took longer to change. From Table 4.2 it is apparent that post-task but not task- values were high. This provided evidence for a metabolic lag, also evidenced from the post-task values and not task values showing highest consistent changes from the baseline. From both Table 4.2 and Table 4.3, we found that the brain regions in the prefrontal

cortex and not in the motor cortex were thus participating (via activation or deactivation) in responses to the Stroop tasks similar to what have been found earlier (Plenger et al., 2016; Giles et al., 2014).

Out of all channels, B1, B2, A5, A6 in prefrontal cortex showed the highest task-responsiveness as shown by the high Cohen's D measures calculated in each subject (Table 4.2 and Table 4.3). High effect sizes were found in about 30% of the subjects. However, that could be because those channels had better contact with the skin. The task responsiveness was better (higher effect sizes) for the oxy-, total- and diff-Hb signals compared to the baseline but not for the deoxy-Hb. This was attributed to the metabolic lag where systemic changes occurred first and had higher effect size than the neuronal changes, which occurred later. It also explains why previous studies reported only systemic (oxy-Hb) changes after exercise (Giles et al., 2014; Tempest et al., 2014; Lambrick et al., 2016; Byun et al., 2014; Yanagisawa et al., 2010) and in response to the Stroop tasks (Plenger et al., 2016). However, this did not necessarily mean that the neuronal firing was not taking place, it could mean that the neuronal firing occurred after a lag compared to the systemic changes. To confirm this, the later tests on correlation of performance in terms of accuracy and RT to the hemodynamics were conducted in order to determine if the changes were truly systemic or neuronal.

To confirm the correspondence of the blood flow changes to the behavioral data evident in trial-averaged hemodynamic response, additional correlations were investigated by correlating the hemodynamics to the RT and mistakes using Spearman’s Ranked Order correlations. The correlations were done both at the individual level, for ecological validation (Brunswick, 1956; Parsons, 2015; Smith, 2012; Kazdin, 2010), and at the group level. Non-parametric Spearman’s Rho

correlations were used at the individual level for all the subjects so that the correlations were normalized.

The interpretation from Figure 4.7 is that oxygen extraction was higher in Channel A4 at right PFC for that subject when fewer mistakes were made. This indicates possible benefit to executive function and fewer errors made with increases in oxygen extraction after exercise. Fewer mistakes in the incongruent Stroop task and the activation of channel A4 at right PFC immediately after exercise (Figure 5.2) implied higher oxygen extraction at this brain region after exercise helped the subject make fewer mistakes.

For both the before- and after-exercise conditions (Figure 4.7) in the same subject and same brain location channel A4, deoxy-Hb was aged behind oxy-Hb. This means that the metabolic response of deoxy-Hb came after oxy-Hb. This explained why in the raw data (Figure 4.7) the oxy-Hb values fluctuated more than the deoxy-Hb. Deoxy-Hb took longer to change, because this metabolic response had a lag. Moreover, the after-exercise phase plot was steeper than the before exercise (Figure 4.7), meaning that the oxygen demand (deoxy-Hb) was not met by the oxygen delivered (oxy-Hb) after exercise — also pointing to the greater activation of neurons in this region after exercise. This could explain how exercise may improve executive function (in incongruent Stroop task involving conflict-resolution) due to higher activation of neurons in the right PFC.

The summary of Rho outcomes for the rest controls revealed left PFC activities in correlation with the RTs in both the congruent and incongruent Stroop tasks (Table 4.4). Right PFC and MC activities are correlated with mistakes made both in the congruent and incongruent. The hemodynamic changes were neuronal (deoxy-Hb and diff-Hb) in correlation with the behavioral data in the Stroop tasks, however, neuronal

changes seem to follow the systemic changes (total-Hb) atleast for the congruent Stroop tasks. A metabolic lag could explain the delay in the neuronal response from the systemic response.

Left PFC and pre-MC were best correlated with the RT of both congruent and incongruent Stroop tasks (Table 4.4). This matched the earlier findings of similar brain regions participating in the Stroop tasks (Plenger et al., 2016; Byun et al., 2014; Yanagisawa et al., 2010).

Percentage of subjects showing correlation of the brain hemodynamics with the mistakes in the incongruent Stroop task dropped after repeated exposure (Table 4.4). This result is consistent with the speed-accuracy modelling result in section 2.7.1 that showed no correlation of the speed to the accuracy in the after session indicating less attentional and hemodynamic resources to the task after repeated exposure (habituation).

Right PFC and primary MC were correlated with mistakes during the congruent Stroop tasks and the percentage of subjects making mistakes in the congruent Stroop tasks were lower than incongruent Stroop tasks (Table 4.4). This result was expected, as incongruent Stroop task was more difficult than congruent Stroop task so more people made mistakes in the incongruent Stroop tasks compared to the congruent Stroop tasks. Furthermore, whenever mistakes were made for the congruent Stroop task, the right PFC and motor cortex (insula) were active and these regions have been correlated with emotional regulation (Luo et al., 2014; Etkin et al., 2013; Grandjean et al., 2012; Hutcherson et al., 2012; Clark et al., 2008; Bechara et al., 2002; Critchley et al., 2000).

The hemodynamic changes correlated with the behavioral data of both RT and mistakes for the incongruent Stroop tasks were neuronal, but for the congruent Stroop

tasks were systemic (Table 4.4). This could have been because of the more difficult nature of the incongruent Stroop task, which required greater neuronal firing and possibly neurotransmitter activities.

Fewer subjects' incongruent Stroop task RT correlated with the pre-MC after exercise and for the ones that did the hemodynamic changes were neuronal (Table 4.5). This indicated that the subjects were more disinhibited after exercise, leading to faster RT. Moreover, the neuronal firing was high in the pre-MC and that correlated with faster RT (negative correlations, Table 4.5). Left PFC was most correlated to mistakes; pre-MC was most correlated to the incongruent RT in the Stroop tasks even after exercise (Table 4.5). Percentage correlation to the behavioral data mostly decreased except for mistakes in congruent Stroop tasks indicating an uncoupling of hemodynamic responses to the cognitive performance after exercise. This could explain why the accuracy in the Stroop task after exercise did not result in any significant improvement. In addition, after exercise, the hemodynamic changes correlated with mistakes were systemic (oxy-Hb) and at left PFC, and hemodynamic changes correlated with RT were neuronal (deoxy-Hb) and at pre-MC. The systemic hemodynamic changes in oxy-Hb after exercise has also been reported in previous research (Giles et al., 2014; Tempest et al., 2014; Lambrick et al., 2016; Byun et al., 2014; Yanagisawa et al., 2010).

These data indicated that exercise uncoupled the correlation between PFC hemodynamics and RT, and that again could be an outcome of automaticity and disinhibition (more impulsivity), which is essentially a sympathetic response.

This supports hypothesis *H3A* that neural activities during Stroop tasks correlated with the neuronal hemodynamic responses, both at the prefrontal and motor cortices and that these changes were also reflected following exercise *H3B*- especially

for error related changes. In summary, the neuronal hemodynamic responses assuming scalar population, coding did predict the cognitive behavioral responses in Stroop tasks (*H3A)*, and following exercise the mistakes correlated better with systemic hemodynamic responses at left PFC, and the RT correlated better with pre-MC neuronal hemodynamic responses especially for the incongruent Stroop tasks compared to the congruent Stroop tasks (*H3B)*.

4.6 Conclusions and Future Directions

The results of the current study matched the previous findings of increased blood perfusion and oxygenation at the PFC immediately after exercise, identified using fNIRS technology (Lambrick et al.,2016; Byun et al., 2014; Yanagisawa et al., 2010; Giles et al., 2014; Tempest et al., 2014). However, the present study takes the research further by showing that after exercise oxygenation and neuronal activities at the motor cortices in addition to PFC was also important in its correlation to RT. Thus, the faster RT immediately after exercise was correlated with the higher MC and PFC metabolism changes. We interpreted that higher dis-inhibition immediately after exercise and greater automaticity lead to faster RT responses.

Systemic changes at the PFC correlated with accuracy after exercise. This meant after exercise, some subjects performed poorly and others performed well, depending on whether there was sufficient neuronal firing in the PFC. Insufficient PFC activities after exercise lead to further disinhibition and more mistakes. Signal noise unrelated to the functional activation and caused by systemic changes including exercise could cause uncoupling of the hemodynamic response from cognition (Scholkmann et al., 2014). Thus, we concluded that exercise did <u>not</u> effectively

improve executive function although subjects had faster RT after exercise, and that correlated with the hemodynamic responses per our hypothesis *H3B*.

Usually, the oxy-Hb responses were opposite to those in deoxy-Hb - that is, oxygen supply and demand were anti-correlated, but after exercise both oxy- and deoxy-Hb showed similar positive deflections. Usually oxy and deoxy –Hb responses were anti-correlated if it was neutrally evoked (Scholkmann et al., 2014). This indicates a higher demand of oxygen not being met by the oxygen delivered as demonstrated in the single subject in Figure 4.7. It was concluded that $PaCO_2$ (partial pressure of carbon dioxide in the arterial blood) increased with both speech and exercise and this hypercapnia most likely led to an increase in cerebral blood flow that led to improvement in cognition in terms of both accuracy and RT for that subject after exercise.

To conclude, exercise specific changes cannot be generalized to improve executive function in the overall population. Uncoupling of cerebral hemodynamics in PFC to mistakes was observed after exercise in majority of the subjects. Furthermore, exercise-specific neuronal hemodynamic correlations with both PFC and MC corresponded to faster RT for both congruent and incongruent Stroop tasks.

CHAPTER 5

CRITIQUE OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY (fNIRS)

5.1 fNIRS Data Collection and Analyses – Current Study

The fNIRS data in the current study (Chapters 4 and 5) were collected from the emitters and detectors located in a cap fitted to each subject (Figure 4.1). The original temporal montage on which the calibration settings were based is depicted in Figure 5.1.

The optodes were placed down by one optode location than the way in which the data was originally calibrated and processed by the software Boxy (dependent on modified Beer-lambert Law as described in Chapter 4). This misalignment was created during the re-assembly of the machine, but did not emerge until after the experiments were concluded. Thus, the Boxy calculations of oxy-Hb and deoxy-Hb was not accurate but nonetheless were precisely relative measures. However, some inaccuracy is inherent in this technique since there is about 15% variability in the differential path length factor (Equation 4.2) within subjects (Scholkmann et al., 2014; Duncan et al., 1995). We did group averages which should have averaged out the error due to differential path length factor (Scholkmann et al., 2014).

Moreover, the placement of the optode caps will inevitably vary from subject to subject because of the unique head geometry of each person. Placement of optodes vary between subjects because of differences in geometry and differences in tying of the headgear, making the quantification of fNIRS signal non-uniform (Hoshi et al., 2005; Kohl-Bareis et al., 2002). Additionally, the caps were held on by Velcro straps, which might have become loose with head movement and with sweat, especially for the after-exercise experiment. Despite these potential sources of variation, the focus of this study was on the physiological effects as described in section 4.2.3. Thus, the

relative changes of the hemodynamic measures in the present study should not be compromised. Again, the error due to source detector separation calculations in Equation 4.2 (modified Beer-Lambert Law calculations from the Boxy software) should have been addressed with both single subject and then group analysis of the relative physiological measures.

Additional sources of error from fNIRS include extracerebral systemic changes in fNIRI measurements from the scalp skin, subcutaneous tissue, aponeurosis, connective tissue, periosteum, cranium, meninges, cerebrospinal fluid (Zaidi et al., 2015; Scholkmann et al., 2014). Variability especially in the oxy-Hb fNIRS signal could have been artifacts of vasomotion (variations in blood vessel diameter) associated with spontaneous hemodynamic oscillations related to heart beat (~ 1 Hz) or breathing (Zaidi et al., 2015). However, Kirilina et al. (2012) indicated that stimulus or task evoked sympathetic arterial vasoconstriction influences fNIRS and these spontaneous hemodynamic fluctuations were found to be neuronal brain activity related (Hoshi et al., 1998). In addition, these extra cerebral noises should have been filtered out using the in-built band-pass filtering technique from the ISS Imagent equipment software Boxy. Moreover, I used the conventional block (time-triggered) averaging technique where I averaged the time-locked hemodynamic signals to the presented stimuli (Baseline, Task, Post-Baseline) which should have addressed the extra-cerebral noise in the data. We used multiple detectors and sources to obtain the 2 D topographic images as in Figure 4.1 and Figure 5.1, and then we used multivariate analysis on the univariate measures from the different channels. This was an efficient way to improve the reliability of the measures (Scholkmann et al., 2014; Patel et al., 2011). HR data was regressed out in the data analysis by keeping HR as co-variate in the ANCOVA models and thus in this way, neuronal and systemic evoked data were separated from

non-evoked data oscillations due to heart beat changes.

Optode placement in fNIRS studies, and the blood oxygenation signals they generate, could be reflective of a specific group of neurons that fire in the same direction or from a group of neurons that are firing in different and/or opposite directions with a predominate direction by the majority of neurons. Such patterns of neuron firing potentially impacts the calculations used in fNIRS studies, resulting in a scalar sum of the neural firing (scalar population coding) instead of a vector sum of the population of neurons (refer to section 1.3).

In addition to the spatial issue revolving around optode placement, there is also a temporal aspect. Neural activity is measured as a time-averaged signal in response to the cognitive stimulus. In the present study, a rate-coding estimate of the neural activity was derived. It is possible that the neurons were coding in a different fashion, for example displaying temporal coding.

The present study documented a delay in the metabolic response, which was different for different parts of the brain. Thus, for each brain region greater accuracy will derive from quantifying the delay in the hemodynamic signals.

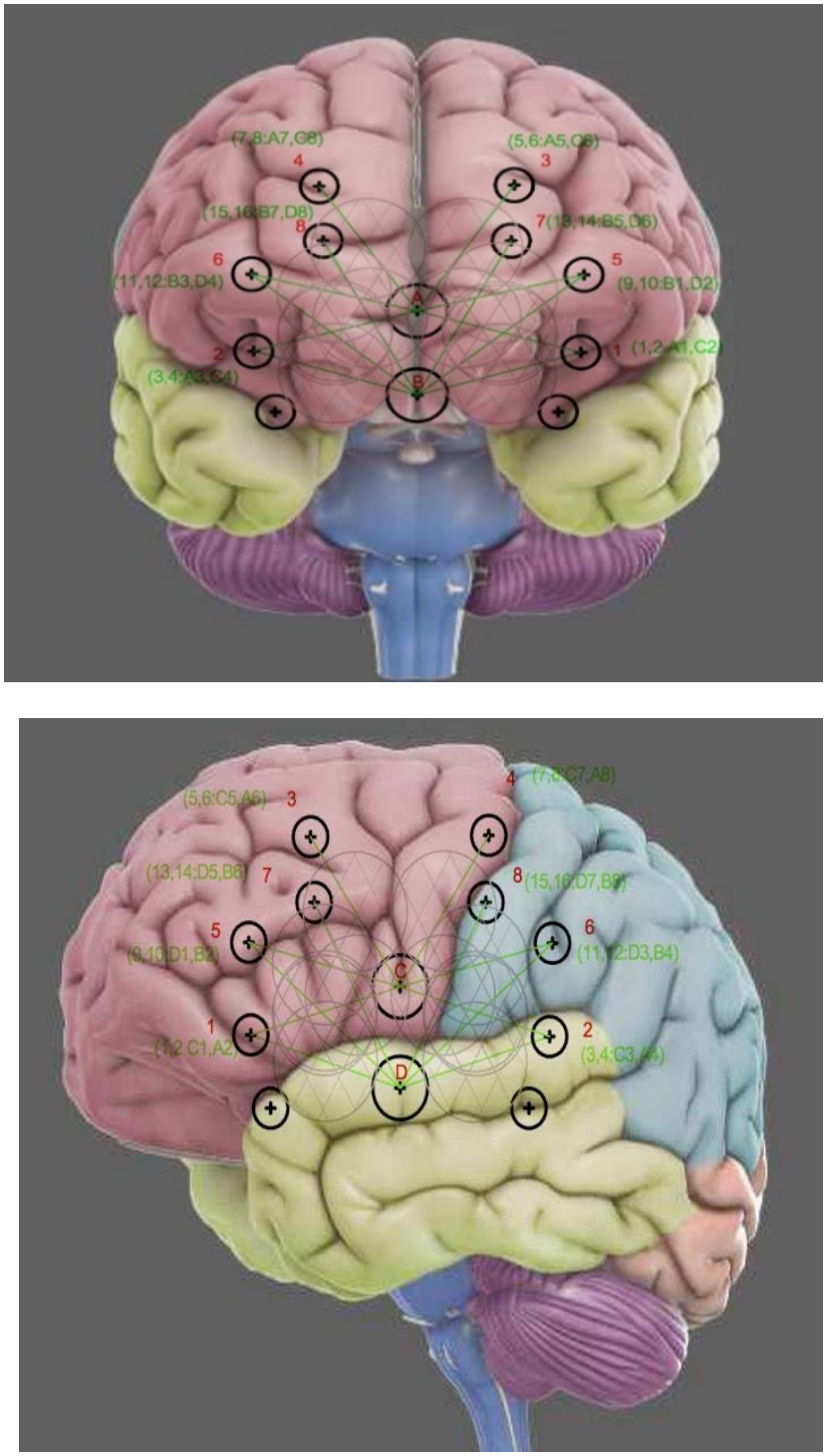


Figure 5.1. Original optode placement on the fNIRS cap-- Prefrontal cortex PFC (A), motor cortex MC (B) Smaller circles represented the emitters and bigger circles represented the detectors. The green lines were the channels (created by Tam & Zouridakis, 2014).

5.2 Additional Known Limitations of fNIRS

fNIRS has a low spatial resolution, measuring only up to 2 cm depth within brain tissue - fNIRS cannot measure blood oxygenation in deeper layers. The fNIRS signal passes through the scalp and skull before reaching blood in the brain tissues, themselves (Minati et al., 2011). Therefore, it has been suggested that changes in extra-cerebral blood flow at the scalp and skull can influence the determination of cerebral hemodynamics (Hoshi et al., 2005; Kohl-Bareis et al., 2002).

5.3 Comparing Other Brain Imaging Techniques with fNIRS

5.3.1 Functional Magnetic Resonance Imaging (fMRI)

As in fNIRS, neurovascular coupling is the basic principle underlying fMRI technology. fMRI measures what is termed the blood oxygenation level dependent (BOLD) signal (Logothetis et al., 2004). The working principle of fMRI is based upon magnetic differences between oxy-Hb and deoxy-Hb signals, with the deoxy-Hb becoming strongly paramagnetic. During neuronal activation, the localized increases in rCBF increase blood oxygenation and consequently reduce deoxy-Hb, with a subsequent increase in the magnetic resonance signal. The spatial resolution of fMRI is 3-4 mm. After excitatory neurotransmission induced by glutamates released by neurons and astrocytes, the BOLD signal may increase. It is unclear how BOLD signal changes correspond to the changes in inhibitory neurotransmitters like GABA (γ-aminobutyric acid). Early in the use of fMRI technology it was thought that blood flow increased due to the neuronal activity because of a need for oxygen or glucose (a feedback mechanism) (Casey et al., 2002). However, more recent research suggests a feedforward mechanism of functional hyperemia, producing an increase in regional blood flow when a cognitive stimulus is presented (Otsu et al., 2015).

5.3.1.1 fMRI Use in Decision Making Tasks

fMRI has been conducted on patients with lesions in ventromedial or vmPFC. These patients performed poorly in the Cambridge Gamble Task, demonstrating risky decision making (Clark et al., 2008). Planning and response inhibition – two decision making tasks – were evaluated using MRI scan and a correlation was found with activity in the ventromedial prefrontal cortex (PFC) (Hutcherson et al., 2012). fMRI studies for Stroop tasks revealed the importance of the ACC (Anterior Cingulate Cortex) for response conflict-detection and response monitoring in the incongruent vs. congruent tasks. This demonstrates the importance of the dorsolateral prefrontal cortex (DLPFC) for focusing on task-relevant information or selective attention (MacDonald et al., 2000). Moreover, Grandjean et al. (2012) revealed additional participation of the insula during the incongruent Stroop tasks related to emotional regulation.

5.3.1.2 Comparing fMRI to fNIRS

In principal, both fNIRS and fMRI measure the cerebral metabolic rate (utilization of oxygen resulting from ionic pump activity in neurons). The main advantage of fMRI is that it gives a better spatial resolution compared to fNIRS (Cui et al., 2011). However, a disadvantage of fMRI is that the regional rCBF measured by fMRI only reveals deoxy-Hb levels (Anderson et al., 2014). In contrast, fNIRS measures both oxy and deoxy-Hb, providing a clearer picture of the rCBF associated with a functional state and corresponding physiological cortical changes (Anderson et al., 2014; León-Domínguez et al., 2012; Boas et al., 2003). The sensitivity of the fNIRS is also better than fMRI, as a large group of neurons must be firing together before generating a BOLD signal (fMRI) corresponding to a drop in deoxy-Hb

(Tranquillo, 2008). In addition, deoxy-Hb can only be detected in capillaries and venous blood with fMRI. Yet, the oxy-Hb measurement that is additionally obtained by fNIRS can be detected not only in the superficial arteries, but also in the veins and microvasculature (capillaries). This allows a more comprehensive measure of oxygen utilization and subsequent neuronal activity in the brain (Tam & Zouridakis, 2014; Culver et al., 2005). In addition, fNIRS signals have better temporal resolution (~10 ms) allowing measurement of transient activity and, therefore, and so depicting more real-time neural activity (Boas et al., 2003). Other advantages of fNIRS over fMRI include inexpensiveness, lack of sensitivity to body movements, and portability (Fujiki et al., 2014). NIRS can endure subject movement to a bigger degree than fMRI given that the subject wearing the NIRS head probe remains attached to the head of the subject (Huppert et al., 2009).

5.3.2 Electroencephalogram (EEG)

The electroencephalogram (EEG) measures the synchronicity of the electrical activity of all the neurons as detected between two points on the surface of the skull. Either electrodes are attached to a subject's scalp using invasive techniques or electrodes are applied as a wearable head cap using non-invasive techniques (Sahinoglu et al., 2016; Ergen et al., 2014; Bunge & Kahn, 2009). The EEG waves are the vector sum (directional) of all electrical activity (both excitatory and inhibitory). That is, the EEG adds EPSPs and IPSPs (graded excitatory and inhibitory post-synaptic potentials generated by the electric dipoles between the soma and the dendrites) in all orientations. The EEG is usually recorded from the superficial cortico-pyramidal neurons close to the skull (Luck, 2005). The same neurons carry out multiple functions depending on which synapse is active (Sahinoglu et al., 2016;

Ergen et al., 2014; Bunge & Kahn, 2009).

In the time-domain ERP (Event Related Potential) paradigm, grand-averaged waveforms are measured for multiple trials and multiple subjects. These measures consist of time-locked and phase-locked ERP waves in response to the stimulus, which can be sensory like visual or auditory, or even post-perceptual higher-order cognitive task related (Sahinoglu et al., 2016; Ergen et al., 2014). The signal-averaging procedure in ERP removes fidget-related (extraneous, non-task related) noise in the data with noise amplitudes greater than 90 μV (Ergen et al., 2014).

In the paradigm for EEG time-frequency domain, the resulting time-frequency band waves, such as delta (1-3 Hz), theta (4-7 Hz), alpha (8-14 Hz), beta (15-30 Hz) , and gamma (31-60 Hz), are characteristic signatures of the neural responses when the stimulus is presented, for example, presentation of a Stroop color-word stimulus (Ergen et al., 2014). EEG time-frequency waves have also been used for measuring attention during functional tasks in ADHD subjects (Fong et al., 2016).

5.3.2.1 Event Related Potential Waves and Their Cognition Correlates

5.3.2.1.1 P300

P300 is the positive deflection component wave of event related potential (ERP) found in an “oddball” paradigm when a subject spots a “target” stimulus (the oddball) that appear randomly among a train of “regular” standard stimuli (Picton et al., 1992). P300 peaks at 300 ms or more after a stimulus is presented. The amplitude of the P300 wave increases with the lower probability of seeing the target stimulus and higher discriminability or visibility of the targets. A shorter amplitude of P300 indicates making more mistakes or less accuracy, and was found when subjects were not paying attention (Medvidovic et al., 2013; Sur & Sinha, 2009). The latencies of

the P300 wave increase when targets are harder to discriminate from the standards, meaning that the P300 latency measures the time taken for response inhibition. The shorter the latency, the better the speed of response classification or, in other words, the speed of the evaluation of the stimulus (Medvidovic et al., 2013; Sur & Sinha, 2009). Thus, P300 is a neural signature of attention (selecting the main stimulus from the irrelevant stimulus) and is widely used in the odd-ball paradigm studies where the probability of presenting the relevant stimulus is lower than the presentation of the irrelevant stimulus (Luck, 2005).

5.3.2.1.2 N450

N450 is the negative deflection component found at 450 ms after the presentation of the stimulus. These signals are used to detect the semantic conflicts between the color and the word in incongruent Stroop tasks (Ergen et al., 2014; Szucs & Soltesz, 2012; Liotti et al., 2000). A similar N400 component has also been found in the semantic priming literature (Ortu et al., 2013), where a more negative deflection represented detection of semantic conflict when the subjects was not expecting a certain word (Sur & Sinha, 2009).

5.3.2.1.3 Sensory *P1, P2*

In response to sensory stimuli such as visual or auditory, there is a positive deflection component 100-200 ms after stimulus presentation (Sur & Sinha, 2009; Luck, 2005).

5.3.2.1.4 Error Related Negativity (ERN)

ERN detects the number of errors committed by the subject. There is a higher

negative deflection at 200 ms from the stimulus presentation for the paradigm where subjects make more errors (Sur & Sinha, 2009). These ERN studies are popular in Go-NoGo, Flanker and Stroop paradigms (Meyer et al., 2013).

5.3.2.2 EEG and Stroop Effect

The ERP paradigm determines physiological mechanisms underlying the higher reaction time and more errors characteristic of the incongruent Stroop task task compared to the congruent Stroop task (Sahinoglu & Dogan, 2016). EEG studies have helped us understand that the Stroop effect was not merely an outcome of the differences in sensory processing between the incongruent and congruent stimuli. Instead, the Stroop effect was an outcome of differences in the response conflict monitoring and the selective attention between the incongruent and the congruent Stroop tasks (Luck ,2005; Liotti et al., 2000; Szucs & Soltesz, 2012; Ergen et al., 2014). These inferences on reaction time differences in incongruent vs. congruent Stroop tasks were possible due to the excellent temporal resolution of EEG. Unfortunately, due to poor spatial localizations, it is not possible to infer anatomically the structures involved in cognition using EEG (Luck, 2005).

The amplitude of the N450 ERP waves for incongruent stimuli was found to be more negative compared to the congruent stimuli (Liotti M et al., 2000. This indicates the use of greater attentional resources for the incongruent task involving response selection delays, due to the semantic conflict between the word and the color. This finding on the N450 wave has been subsequently replicated in additional studies (Szucs & Soltesz, 2012; Ergen, 2014). Some studies challenged this finding and suggested that what was being recorded between 300-400 ms was nothing more than a component of P300 wave called P3b instead of N450. Moreover, this wave was of

smaller magnitude for the incongruent Stroop task compared to the congruent (Zurrón et al., 2009). Since the timing was still the same (around 450 ms) irrespective of the name of the deflection wave, the semantic conflict processing was consistently observed at around 450 ms.

Most studies report that the latency of the P300 component is not different between the congruent and incongruent Stroop tasks. This indicates that the processing of the color and word occurs in parallel. The interference arising from the competition among conflicting (congruent versus incongruent) responses occurs in the response monitoring and response production stages after the P300 had been elicited. The Stroop effect on reaction time was produced after the evaluation of the stimulus, meaning that the latency of the P300 wave was independent of the reaction time. Smaller amplitude of P300 was noted in the left parietal region compared to the right in response to the incongruent stimuli. This indicates a lateralization component with the right parietal region being more active in suppressing color-word conflicts (West et al., 1999). Some studies found that P300 waveform showed larger amplitude immediately after exercise compared to the rest (control), and the latency of P300 for the incongruent trials was longer compared to the congruent trials (Hillman C. et al., 2009). Other studies found that the ERN component showed higher negativity for the incongruent stimuli where the subject made more mistakes (Meyer et al., 2013).

Time-frequency domain EEG studies by Ergen et al., (2014) report that the event-evoked delta waves at 300-450 ms showed larger amplitude for the congruent Stroop tasks, compared to the incongruent Stroop tasks. These were interpreted as differences in the response conflict. Phase and non-phase-locked theta waves at 300-700 ms showed higher amplitude for the incongruent rather compared to the congruent Stroop tasks, indicating differences in the response selection phase in the incongruent

tasks compared to the congruent Stroop tasks. Higher desynchronization of the alpha waves at 100-200 ms occurs for the incongruent Stroop stimuli, indicating inhibition control of task-irrelevant visual stimuli (Ergen et al, 2014).

5.3.2.3 EEG in Comparison to fNIRS

Supplementing functional brain imaging techniques like fNIRS, P300 studies have been used to detect changes in amplitude and latencies for investigating decision making responses (Linden et al., 2005). EEG signatures cannot be mapped back to the brain structure or localized to a particular brain region since these signals are diffused and not location-specific (Luck, 2005). NIRS has better spatial resolution compared to the EEG/ERP (Lenkov et al., 2013) techniques. Yet, by using a higher number of electrodes (for example 128 as opposed to 30 electrodes) for EEG recordings and by using triangulation techniques for source localizations, EEG signals could serve better for anatomical studies (Luck, 2005). In addition, the signal-to-noise ratio for EEG is higher than that of fNIRS (Bunge & Kahn, 2009).

5.3.3 Transcranial Diffuse Correlation Spectroscopy (tDCS)

Like fNIRS, tDCS is an optical imaging technique, which gives a measure of cerebral blood flow by measuring by photon counting and thus estimating the microvascular blood flow in the middle cerebral artery (Kim N. M. et al., 2010). When red blood cells move, one can obtain the velocity and flow measurements. Using tDCS, right DLPFC was associated with riskier decision making in healthy adults performing cognitive tasks like balloon analogue risk tasks (BART) and Roger's risk tasks (Hang et al., 2015). Together with fNIRS, tDCS measurement better represents the CBF and oxygen utilization in the brain (Pei-Yi Lin et al., 2013).

5.4 Future Directions.

Any conclusion drawn based on the above data should be repeated using more sophisticated fNIRS equipment. Future analysis should be repeated assuming vector population coding. Different spatio-temporal analyses could be done in future studies.

This study also recommends improvement in the fNIRS technology so that it is capable of addressing the metabolic lag in the deoxy-Hb response compared to the oxy-Hb response once the lag has been quantified.

CHAPTER 6

GENERAL CONCLUSIONS

This study has examined the cortical hemodynamic responses in prefrontal and motor cortex and HR while the subjects performed Stroop tasks before and after exercise. The results were compared to before- and after- exercise and control (rest) experiments.

The general findings are that:

- Exercise specific changes in RT and mistakes in Stroop tasks. This study found that exercise improved reaction times but not accuracy in the cognitive Stroop tests. Moreover, high-BMI ADHD females (Appendix A) made more mistakes immediately after exercise.

- Exercise specific changes in HR during Stroop tasks. The increase in HR after exercise correlated with faster RT and better accuracy.

- Neural encoding. Assuming the neurons are encoding the Stroop tasks via rate coding, the present study has analyzed the hemodynamic signals using time-averages for the pre-task baseline, during task and after-task values. Therefore, if the neural data are encoded differently than the rate coding, then the conclusions may differ.

- Metabolic lag. Hemodynamic responses showed a metabolic lag for deoxy-Hb compared to oxy-Hb. In future studies this lag needs to be quantified to make accurate predictions of neural activity using fNIRS technology.

- Hemodynamic responses. PFC showed the most task-responsive systemic changes from the baseline. The hemodynamic responses were opposite for the right and left PFC, and opposite for congruent and incongruent Stroop tasks.

- Hemodynamic responses after exercise. PFC showed the highest effect

sizes of Stroop task-responsive systemic hemodynamic changes from baseline. Although, when trial-averaged hemodynamic responses were compared before and after exercise, PFC showed most significant ($p<0.001$) neuronal hemodynamic changes which were opposite for right and left PFC, and opposite for congruent and incongruent Stroop tasks. Correlating the RT and mistakes with hemodynamics for both the Stroop tasks, revealed that after exercise, neuronal hemodynamic changes occurred at both PFC and MC associated with faster RT ($p<0.05$), and systemic hemodynamic responses occurred at PFC correlated ($p<0.05$) with mistakes. Systemic changes at PFC correlated with higher mistakes especially in the high-BMI, ADHD females (Appendix A). This implied hyperactivity and insufficient inhibition-control due to insufficient neural activity at the PFC especially in the high-BMI, ADHD females.

- Data distributions and analytical approaches: Reaction time data and accuracy showed non-normal distribution, indicating the use of median rather than mean values as central tendency measures for future comparative studies. In addition, use of non-parametric statistics for comparative studies like Spearman's ranked correlation was used effectively in the present study.

- Use of non-parametric Spearman's ranked order (Rho) correlations. The correlations were performed on the ten trials in individual subjects first using non-parametric Rho and then the slopes were analyzed over multiple subjects using summary of outcome measures. There was better control over data validation in that we considered task-responsive channels that also correlated with the behavioral data (RT and mistakes) in individual subjects and then we interpreted how exercise affected the correlations at the group level. Moreover, using this approach we accounted for the non-normal distribution of the behavioral data.

- Variability: There was considerable inter-subject variability in both the behavioral and hemodynamic data. The demographics of ADHD status, BMI status or gender by themselves could not explain this variability. Yet, specific interaction effects did moderate the cognitive performance correlated to hemodynamic data. High-BMI, ADHD females performed worse in terms of both RT and accuracy (Appendix A).
- Sample sizes. In the future, increased sample sizes in each group could help elaborate upon the current findings. Especially in order to improve statistical power we would need to have a bigger sample size to address the demographics question.

Lastly, I would like to discuss the concepts of ecological, internal and external validity with respect to my experimental design. Factors that could impact the implications of my research with respect to each of these three validities were outlined as follows.

- Internal Validity. This scientific concept tested the validity of the relationship between the changes in the behavioral data immediately after exercise and the independent variables of changes in hemodynamic variables, demographics. Factors that could have been a threat to internal validation were—
    - Familiarity with the Stroop task (so the thirteen subjects who came back for the study at a later time and repeated the control exercise experiments)
    - Events that may have occurred in their personal lives (although, since we took baseline measurements so we had accounted for it in some form)
    - Instrumentation errors.

- External Validity. This is the concept that validates the extent to which exercise effects applied to the general population beyond the students tested in my study. Since the study had n = 103, however a larger n would have helped validate it externally to the general population, plus since the study was in a lab setting that could also have influenced this.

- Ecological Validity. Now since this concept checks for the reliability of the 'effect' in real life setting, again the lab environment might have affected it. Brunswik (1956) was first to talk about ecological validity, however there are still many debates on how to validate this particular concept. In my study though, we tested for the 'real life effectiveness' of the treatment of exercise and its impact on accuracy in one individual over 10 trials before and after exercise. We also noted how this affected the brain hemodynamic response, and what was the correlation of the hemodynamic response with the changes in the behavioral data by using non-parametric correlations in that individual over the course of 10 trials before and after exercise.

Overall, it can be concluded that immediately after exercise the improvement in speed did not co-vary with the improvement in accuracy. An increase in dis-inhibition associated with higher mistakes after an acute bout of exercise (most likely a sympathetic response) was observed especially in high-BMI ADHD females. Faster RT immediately after exercise was attributed to increased neuronal activities at the PFC and MC. After exercise, there was an uncoupling of cerebral hemodynamics at the PFC with accuracy, and we found more systemic changes at the PFC correlated with more mistakes. In the future, more studies are warranted to confirm this. fNIRS is a powerful technique but has limitations, and more research should be done to quantify these limitations when studying metabolic impacts of exercise on cognition.

APPENDIX

DEMOGRAPHICS DATA

A.1. Introduction.

This was a preliminary data analysis for moderating effects of demographics and we will be able to confirm the findings later with bigger sample and greater statistical power. However, the current results seem promising and added to my understanding of the findings from the dissertation.

A.1.1. Cognition for different demographics.

A.1.1.1. ADHD.

Based on the results of previous equivocal studies, ADHD subjects may improve or perform more poorly in the inhibition-control cognition task, compared to the healthy control subjects. Moreover, the associated neural responses may or may not change after exercise. Aerobic and coordinative aquatic exercise intervention improved inhibition control in ADHD children (n=30, 5-10 years of age) (Chang et al., 2014). This exercise intervention study was 8 weeks in length and both the reaction time and accuracy associated with the Go stimulus (attention task) of a Go/No-Go task illustrated improvement. In addition, acute bouts of moderate intensity aerobic exercise for 30 min in ADHD children showed an improvement in executive function in the Stroop color-word tests by reduction in reaction times only (Chang et al., 2012).

To improve upon these studies, the change in both reaction time and accuracy in the cognitive Stroop task should be tested after aerobic exercise. ADHD adults have shown inefficient interference control and task coordination compared to non-ADHD counterparts in Stroop color-word test (King et al., 2007). ADHD individuals were, on average, 11.4% slower than age-matched controls in Stroop color word test task (Schwartz et al., 2008). With increased age, ADHD females performed better on an attention task (Ernst et al., 1998).

A.1.1.2. BMI (Body Mass Index).

Overall, academic performance improved in a physically active classroom, and there was a negative correlation between BMI (kg/m^2 body surface area) and a physically active curriculum (Donnelly et al., 2011). Elementary grade children with high BMI (>25) who were given 10-15 minutes of moderate-to-vigorous physical activity during academic lessons performed better in fact-based learning tasks such as mathematics and literature (Grieco et al., 2009). Thus, there was an improvement in cognition in the high-BMI populations. Consequently, in the current study it was predicted that BMI mediates exercise effects on cognition.

A.1.1.3. Gender.

The females were faster than males for the incongruent Stroop task when exercising (Baker et al, 2010; Davidson et al., 2003). This is what is also predict in the current analyses.

A.1.2. Differences in cerebral perfusion based on demographics.

A.1.2.1. ADHD.

fNIRS is a valuable neuroimaging technique to measure prefrontal cortical activation for ADHD subjects performing another cognitive taskcalled the Go/NoGo inhibition control task, which is very similar to Stroop task (Nagashima et al., 2014; Monden et al., 2012). Relative to control subjects, ADHD subjects exhibited reduced activation in the right inferior frontal gyrus and the middle frontal gyrus in Go/NoGo tasks (Monden et al., 2012).

In ADHD children with deficits in planning and organizational behavior, lowered regional Cerebral Blood Flow (rCBF) was measured in the striatum putamen, caudate nucleus, and cortico-striato-thalamo cortical loops (Sistino, 2013). This neuro-pathophysiology was also identified in mouse model studies using neurochemical

assays (Thomas et al., 2009). This suggests that for children with ADHD, low rCBF in PFC is correlated with ADHD unless there is a compensatory higher activation (Moser et al., 2009). In inhibitory control tasks, un-medicated ADHD children exhibited reduced brain activation (found using fNIRS) in the right inferior and middle frontal gyrus (ventromedial PFC) compared to healthy controls (Nagashima et al., 2014; Monden et al., 2012).

In adults with ADHD, there is significantly lower cerebral perfusion in the left PFC orbit and pole, and PFC deactivations increased when subjects perform a concentration task (Amen et al., 2008). Reduced bilateral ventrolateral PFC activation occurs in ADHD adults on a working memory letter n-back task (Ehlis et al., 2008). In a gambling card game with long-term gain, ADHD adults differed from healthy controls in the hypo-activation of ventral and dorsolateral PFC and insular regions, and hyper-activation of caudal right anterior cingulate (Ernst et al., 2003). Males with ADHD show higher regional cerebral perfusion in the left caudate nucleus, parietal and frontal regions compared to age-matched controls (O'Gorman et al., 2008). With stimulant medication, the differences in perfusion were normalized in the left caudate nucleus and inferior frontal gyrus, helping ADHD males to become more functional, meaning their cognitive performance closer to their non-ADHD counterparts. The frontal gyrus in ADHD males continues to remained hyper-perfused after treatment with stimulant medication (O'Gorman et al., 2008). Using fNIRS and Stroop interference task, in ADHD boys (age 8-13), compensatory higher oxygen consumption and brain activation occurred in the right dorsolateral PFC (Moser et al., 2009). In adult ADHD females, lower cerebral metabolic rates have been lateralized to the left hemisphere of the frontal and parietal regions (Ernst et al., 1998; Ernst et al., 1997; Zametkin et al., 1993).

A.1.2.2. BMI.

Elevated BMI is associated with decreased rCBF in Brodmann areas 8, 9, 10, 11, 32, 44 (dorsal PFC) and decreased executive-functioning using neuroimaging in otherwise healthy subjects (Willeumier et al., 2011). BMI is negatively correlated with prefrontal metabolic rate in otherwise healthy adults (Volkow et al., 2009). Moreover, obesity (BMI >30 kg/m^2) is correlated with cognitive function impairment while subjects performed Stroop tasks, along with hypo-activation in Brodmann areas 8, 9, 10, 11, 44, 32 (in PFC and ACC) (Volkow et al., 2009). Immediately after exercise, high BMI population shows improved cognition, which has been attributed to improved cerebral perfusion immediately after exercise (Memel et al., 2016).

A.1.2.3. Gender.

Regional cerebral blood flow (rCBF) at resting level (without performing any cognitive task) showed a higher rCBF for healthy females compared to healthy males in the frontal region (Gur et al., 1990).

A.2. Hypotheses.

H1B. After exercise compared to rest, the relative changes in RT and accuracies (behavioral data) will differ between male and female, ADHD and non-ADHD, normal- and high-BMI populations.

H2C. Changes in HR after exercise will alter the cognitive behavioral data distinctly in different populations of high- and normal- BMI, ADHD- and non-ADHD, male and female.

H3C. The brain hemodynamic correlates of cognition will be different between ADHD vs. non-ADHD, normal vs. high-BMI, male vs. female. Also with exercise, the impact on the blood flow and its correlation with cognition will be different in pathological population like high-BMI, ADHD. However, specific demographics impact on blood

flow shall be tested in future with a bigger sample size.

A.3. Methods.

A.3.1. Change in behavioral data after exercise accounting for demographics.

To determine the moderator variable (qualitative factors like ADHD, gender, high- or normal-BMI) that influenced the strength of the relationship between the change in behavioral data (reaction time or accuracy) with the exercise experiment or control rest experiment, a multivariate general linear model of MANOVA (Multivariate Analysis of Variance) was employed. Multiple non-parametric Mann-Whitney U tests or even the non-parametric one-way ANOVA Kruskal-Wallis tests on the absolute values of the non-normally distributed RT data could have been used to compare the effects of exercise from controls. However, that procedure would have caused an inflation in the Type 2 Mistakes rate. The standardized % changes in RT or mistakes were chosen instead of the absolute value differences for the parametric MANOVA test to overcome the problem of the non-normal distribution of the data.

There were 51 females in the exercise experiment and 19 females in the control rest experiment. There were 22 males in exercise and 11 males in control experiment. There were 56 non-ADHD participants in the exercise experiments and 24 non-ADHD participants in control. There were 17 ADHD in exercise experiment and 6 ADHD in rest experiment. There were 52 normal-BMI in the exercise experiments and 17 normal-BMI in control experiment. There were 21 high-BMI in the exercise experiments and 13 high-BMI in control experiment.

The independent factors in the MANOVA model was the experiments (nominal variable- 2 levels: exercise or control). Additional fixed factors to the above MANOVA model was high- or normal- BMI, gender, ADHD status. The objective of this test was to identify the potential main or interaction effects of the above factors on the change

in RT immediately after exercise or rest. The SPSS /EMMEANS command was modified to compare the *Post Hoc* changes using LSD correction,

"/EMMEANS=TABLES(Gender*BMI*ADHD*ExperimentsExerciseRest)

COMPARE (ExperimentsExerciseRest) ADJ (LSD)".

A.3.2. After exercise change in correlation of HR with behavioral data accounting for demographics.

Linear Regression of HR versus behavioral data with BMI (continuous variable) as co-variate was conducted. The purpose of this test was to determine the mediator effects of BMI (continuous).

In addition, Spearman's ranked order correlation (Rho) was conducted in individual subjects to correlate the accuracy and RT to HR data.

A.3.3. After exercise change in trial-averaged hemodynamics with moderating effects of demographics.

The RM-ANCOVA model in SPSS was modified to include the pairwise *post hoc* 'LSD' (least significant differences) comparisons between before and after exercise for the repeated measures moderated by the demographics (results in Appendix), using the following code:

/EMMEANS = TABLES (channels*Hb*stimuli*Gender*BMI*ADHD*time*Exercise) COMPARE (Exercise) ADJ (LSD)

- IV- before or after exercise
- DV- trial averaged hemodynamics for all 24 channels tested separately for congruent and incongruent Stroop tasks
- Additional Fixed factors were:
    - ADHD status - two levels: True or False
    - BMI status – tow levels: high- and normal-
    - Gender - two levels: Female or Male

A.4. Results.

A.4.1 Demographics impact on % changes of behavioral data after rest and exercise.

In the MANOVA, only non-ADHD, normal-BMI females had significantly faster RT immediately after exercise compared to control rest experiment both for the congruent (faster by 6.6±3.15 %, $p<0.05$) and incongruent (faster by 6±2.34 %, $p<0.05$) Stroop tasks. Appendix Figure A.1 depicted the congruent (A) and incongruent (B) % changes in RT immediately after exercise versus rest. Table A.1 summarized the MANOVA *post-hoc* LSD outcome for RT changes after exercise compared to rest in all demographics.

In addition, only high-BMI, ADHD females showed significantly higher mistakes $M=7.5$, $S.E.= 2.06$ after exercise compared to rest controls at $p<0.001$. Appendix Figure A.2 depicted the this significant change in accuracy immediately after exercise compared to rest controls. Table A.2 summarized the MANOVA *post-hoc* LSD outcome for mistakes rate changes after exercise compared to rest in all demographics.

The reason we are calling this preliminary results as the sample size is still small, impacting the power of the statistics used. In future we would need a bigger sample size to confirm this finding that ADHD, high-BMI females are worse in Stroop tasks compared to the non-ADHD, normal-BMI females.

A.4.2 Cardiovascular (HR) correlation to changes in behavioral data after exercise.

Keeping the BMI (continuous variable) as co-variate, we did not see a significant correlation ($p >0.05$) between HR and RT, Accuracy. This indicated that exercise by itself does not improve cognition but BMI was the mediator variable. The data were also analyzed according to the ordinal variables normal- vs.- high BMI. Reaction time for incongruent Stroop tasks became faster ($p<0.01$) and accuracy

improved (p<0.05) as HR increased following exercise for the normal-BMI population. However, changes in HR following exercise did not significantly affect RT (p>0.05) in the high-BMI population. For the normal-BMI population the non-ADHD males and non-ADHD females as well as the males with ADHD performed the congruent Stroop task more slowly (p<0.05). However, the ADHD females actually became faster (p<0.05) with increases in HR after exercise.

Ecological validation in the individual data from a non-ADHD, normal-BMI male (Figure A.3) illustrated that, before exercise, presenting the incongruent Stroop task stimuli for the first time caused the subject's HR to go up with slower response and more mistakes. After exercise, as HR increased, this individual became faster for the Stroop tasks. However, his accuracy for the task did not change.

A.4.3. Trial averaged hemodynamic responses to Stroop task changes after exercise moderated by demographics.

The high-BMI, ADHD females showed the most significant (p<0.01, n=73) systemic (total-Hb) changes after exercise for the congruent Stroop task and the most significant (p<0.001, n=73) systemic (oxy-Hb) hemodynamic changes after exercise for the incongruent Stroop task (Figure A.4). The hemodynamic changes to the Stroop tasks with exercise were bilateral in the PFC and they were opposite for the left and the right PFC. In addition, the hemodynamic responses were opposite for the congruent and incongruent Stroop tasks.

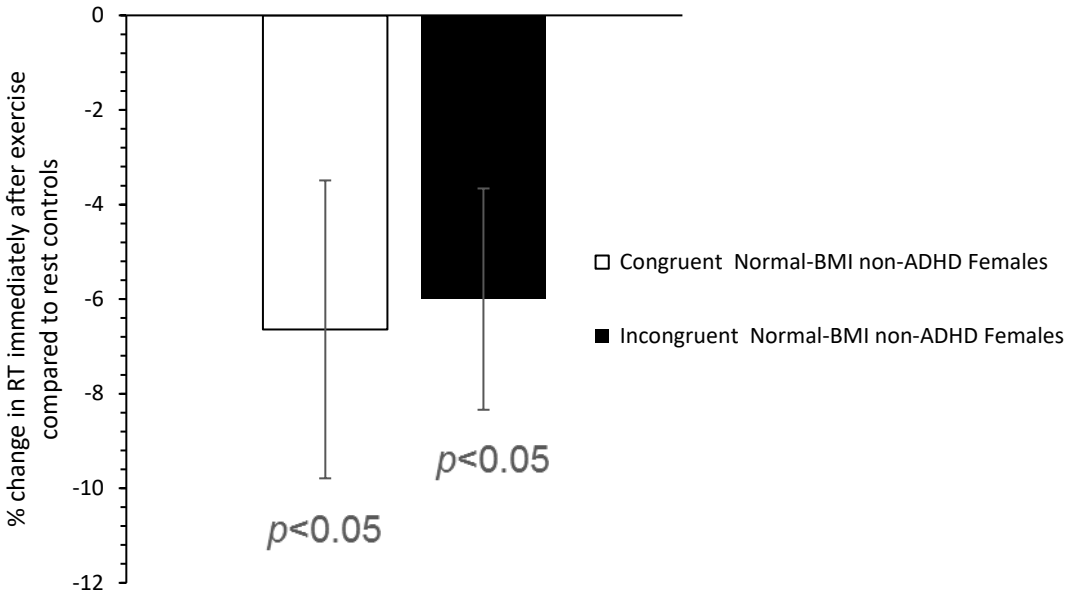


Figure A.1. Percentage change in RT after exercise (demographics). Compared to rest, exercise specific changes in normal-BMI non-ADHD females were significantly (p<0.05) faster by ~6% after exercise, for both congruent (white) and incongruent (black) Stroop tasks.

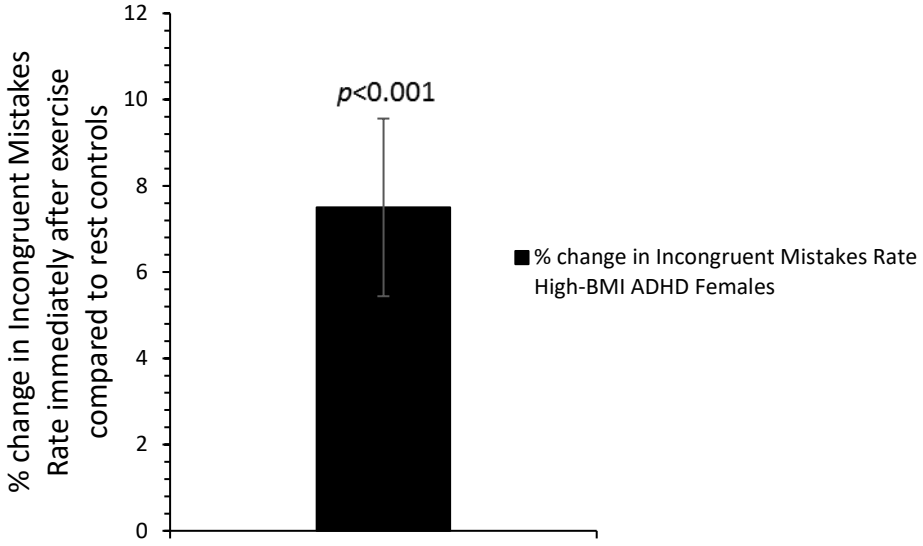


Figure A.2. Percentage change in mistakes rate after exercise (demographics). Compared to rest controls, exercise specific changes in mistakes rate was significantly higher (p<0.001) in high-BMI ADHD females by ~7.5% after exercise, for the incongruent Stroop task.

Table A.1. Demographics impact on % change in RT immediately after exercise compared to rest. The significances were represented by Sig[b] with * being $p<0.05$ significantly faster RT only in non-ADHD, normal BMI females immediately after exercise compared to rest controls.

Dependent Variable				Mean Difference (Exercise-Rest)	Std. Error	Sig.[b]
%Congruent RT	Female	ADHD	normal-BMI	4.564	6.911	.511
			high-BMI	-.866	9.637	.929
		Non-ADHD	normal-BMI	-6.641*	3.148	.038
			high-BMI	-2.076	4.451	.642
	Male	ADHD	normal-BMI	-9.683	7.465	.198
			high-BMI	-8.805	10.557	.407
		Non-ADHD	normal-BMI	6.900	5.564	.218
			high-BMI	-1.212	5.782	.834
%Incongruent RT	Female	ADHD	normal-BMI	4.377	5.148	.397
			high-BMI	-3.025	7.178	.675
		Non-ADHD	normal-BMI	-6.001*	2.344	.012
			high-BMI	-2.684	3.316	.420
	Male	ADHD	normal-BMI	-4.889	5.560	.382
			high-BMI	-4.665	7.863	.555
		Non-ADHD	normal-BMI	7.211	4.144	.085
			high-BMI	-2.573	4.307	.552

Table A.2. Demographics impact on change in % mistakes rate immediately after exercise compared to rest. The significances were represented by Sig[b] with * being $p<0.001$ significantly higher error rates only in ADHD, high-BMI females immediately after exercise compared to rest controls.

Dependent Variable	gender	bmi	adhd	Mean Difference (Exercise-Rest)	Std. Error	Sig.[b]
Change %mistakes rate congruent	Female	normal-BMI	non-ADHD	-.132	.130	.311
			ADHD	-3.969E-15	.278	1.000
		high-BMI	non-ADHD	-.066	.174	.706
			ADHD	-.250	.431	.563
	Male	normal-BMI	non-ADHD	.042	.227	.855
			ADHD	.188	.305	.540
		high-BMI	non-ADHD	.092	.257	.722
			ADHD	.208	.406	.609
Change %mistakes rate incongruent	Female	normal-BMI	non-ADHD	-.148	.619	.811
			ADHD	1.625	1.329	.225
		high-BMI	non-ADHD	-.656	.830	.431
			ADHD	7.500*	2.059	.000
	Male	normal-BMI	non-ADHD	-.875	1.085	.422
			ADHD	1.812	1.456	.217
		high-BMI	non-ADHD	1.275	1.228	.302
			ADHD	-1.437	1.941	.461

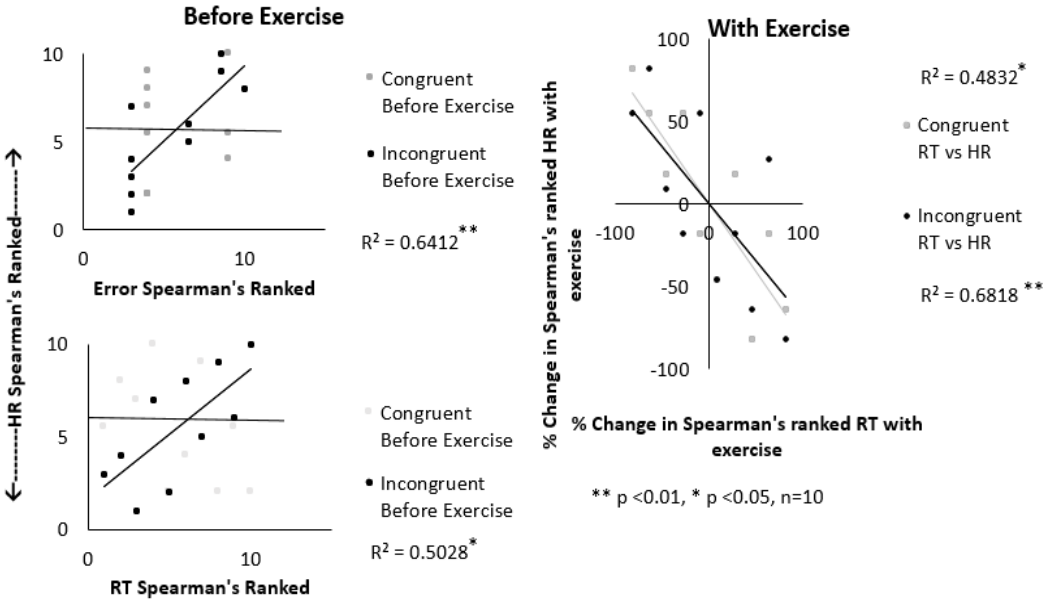
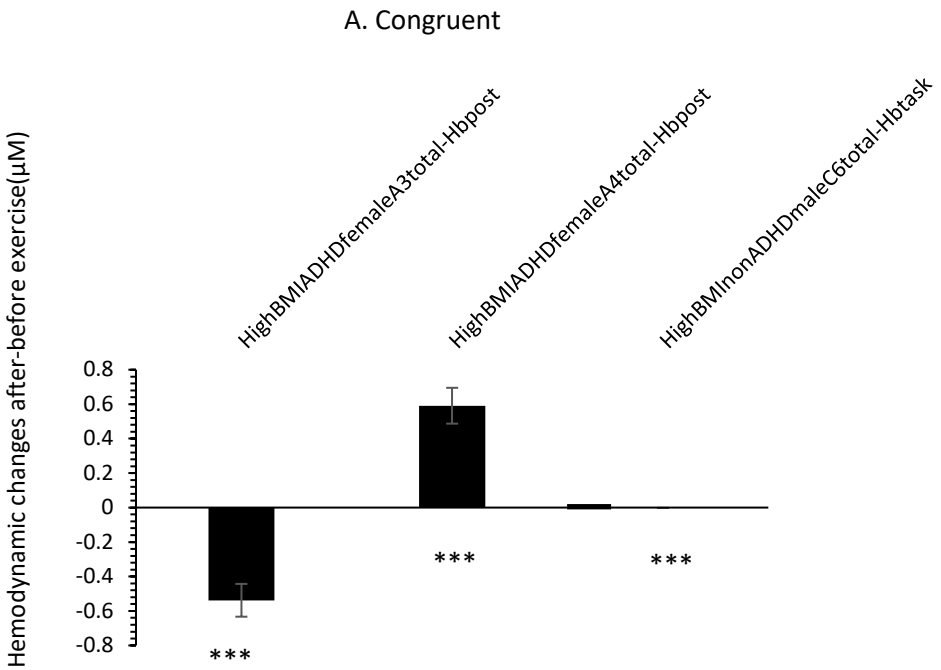


Figure A.3. Individual (male, non-ADHD, normal-BMI) Rho correlation of HR with Behavioral Data. A. Before Exercise, B. Immediately after exercise. ** p<0.01, * p<0.05, n=10, Pearson correlation.



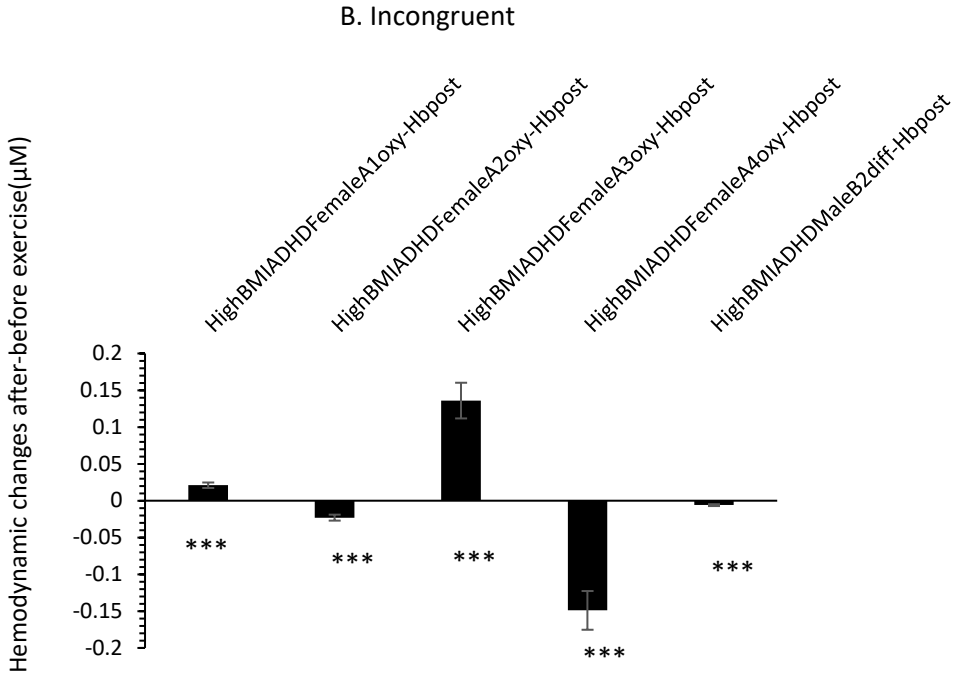


Figure A.4. After-Before Exercise changes in trial-averaged hemodynamic data (demographics). High-BMI ADHD females showed the most significant hemodynamic changes immediately after exercise in the trial averaged hemodynamic responses at the A3 (left PFC) and A4 (right PFC) channels for congruent Stroop task and at A3 and A4, plus, A1 (left PFC) and A2 (right PFC) channels for incongruent Stroop tasks. Responses at Left and right PFC channels were opposite. In addition, hemodynamic responses for congruent and incongruent task were opposite. High-BMI ADHD females also showed significantly worse performance in the cognitive Stroop tasks and these could be related to the significant differences in the systemic hemodynamic data seen above. In other words, blood flow changes occurred in high-BMI ADHD females however, they could not be neuronal and was just systemic because metabolism is challenged in high-BMI, ADHD population.

A.5. Discussion.

In the preliminary results testing hypothesis *H1B* depicted in Appendix Figures A.1 and A.2, and Tables A.1 and A.2, we found that the high-BMI, ADHD females had worse cognition in incongruent Stroop tasks in terms of both mistakes and RT immediately after exercise compared to rest controls, more so than normal-BMI, non-ADHD females. The high-BMI, ADHD females compared to the non-ADHD, normal-BMI females, did not benefit as much from exercise in terms of the change in RT, and the former made more mistakes with exercise. This aligned with Hypothesis # *H1B*, that RT processing depends on the pathophysiological state, and that exercise alone

cannot help improve cognitive performance. Although the sample size was small affecting the power of the statistics used and so we are calling these preliminary findings, yet in future, bigger sample size can confirm this. In the past, Ernst et al. (1997) had found deficits in cerebral metabolism in ADHD females. We extended the current preliminary findings in the behavioral data and correlated it to the brain blood flow data to confirm if indeed poor cerebral metabolism made the cognitive performance worse in ADHD and high-BMI females.

Moreover, in terms of the ADHD status we find that cognitive speed in ADHD, high-BMI was actually better in males compared to females immediately after exercise. The present study thus supports that the acute exercise bout did benefit speed of cognitive performance in adult ADHD men (Fritz & O'Connor, 2016).

In addition, we also found that the RT in congruent and incongruent Stroop tasks was 6% faster immediately after exercise in normal-BMI, non-ADHD females. On the other hand, normal-BMI, non-ADHD males was ~7% slower immediately after exercise compared to rest in the cognitive Stroop tasks. This finding was similar to that reported by Baker et al. (2010) who found aerobic exercise benefitted females more in executive function. Gender differences have been also reported specifically in Stroop task performances (Mekarski et al., 1996) and the findings support that. Mekarski et al. (1996) found that females were faster than males for the incongruent Stroop task requiring conflict-resolution that is choosing the color over the word, as a result of better verbal and fine motor abilities in females.

Testing *H2C,* we saw evidence of an increase in HR correlated with better cognitive performance in normal-BMI individuals; however, brain blood hemodynamics may better answer if the cardiac output correlated with the improvement in cognitive performance. When keeping BMI as a co-variate in the analysis, no correlation was

seen between HR changes immediately after exercise and the reaction time. This meant exercise alone does not cause an improvement in executive functions since high-BMI participants were unable to effectively have systemic blood flow changes with exercise to allow them better executive function. In the normal-BMI population, exercise improved both speed and accuracy for incongruent Stroop tasks. In addition, for the congruent Stroop tasks, ADHD females (with normal BMI) became faster at decision making.

The individual HR data correlation to behavioral data, showing longer RT with more errors the first-time incongruent stimuli was presented (Figure A.3). This was explained by a sympathetic novelty response for the first-time (novel) exposure of the incongruent (difficult) stimulus. However, this response disappeared with subsequent presentations of the incongruent Stroop task stimuli due to habituation to the task.

Trial-averaged hemodynamic changes that were most significantly different between the before and after exercise conditions was in high-BMI, ADHD females who also had performed poorly in the cognitive Stroop tasks (Figure A.4). The hemodynamic changes that high-BMI, ADHD females showed were systemic and not neuronal. This could be attributed to poor metabolic activities and neuronal firing (neurotransmitter release) in the pathophysiological population (Willeumier et al., 2011; Volkow et al., 2009; Ernst et al., 2003). Thus, the metabolic lag is higher in them, so only systemic (cardiovascular) changes in blood flow was achieved with an acute bout of exercise. This systemic change in hemodynamics was not followed by the neuronal hemodynamic changes correlated with cognitive performance as seen in the majority of the sample population data (Chapter 4).

A.6. Conclusions and Future Directions.

Pathophysiological states of high-BMI and ADHD was attributed to worse

performance after exercise compared to rest in females. HR correlated to only the normal-BMI populations' improvement in behavioral response to Stroop task after exercise. Even ADHD females with normal-BMI cognitively benefitted with an increase in HR after an acute bout of aerobic exercise. During Stroop tasks, high-BMI ADHD females showed systemic but not neuronal changes in the hemodynamic data after exercise. This pathophysiological population also have performed worse in cognitive Stroop tasks and such could be attributed to the neuronal hemodynamic changes not following the systemic changes after exercise resulting in an uncoupling of the hemodynamic response from the behavioral Stroop task response in the high-BMI, ADHD females. Right PFC activation was altered during Stroop tasks in ADHD (Jourdan et al., 2009). This meant exercise specifically affected speed of the conflict-resolution decision making incongruent Stroop task by changing the total perfusion. Then, when not engaging in cognition, subjects made more mistakes in the congruent Stroop task correlated to changes in oxygenation at the motor cortex. There was an uncoupling of hemodynamics with behavioral data, after exercise. Exercise specific effects appeared to be sympathetic responses that often compromised the performance of cognitive tasks.

Since these were correlational studies and not causal, future work with larger sample size, and better experimental design controls would confirm these preliminary findings.

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