The influence of an acute bout of aerobic exercise on cortical contributions to motor preparation and execution

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the Thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Increasing evidence supports the use of physical activity for modifying brain activity and overall neurological health (Hillman et al, 2008). Specifically, aerobic exercise appears to improve cognitive efficacy with regards to decisional oddball tasks shown through the P300, whose amplitude and latency is augmented (Magnié et al., 2000). Furthermore, the effects of an acute bout of aerobic exercise on cardiovascular function are well established and are sustained following exercise cessation. Based on these findings, we proposed that (1) an acute bout of exercise may modulate movement-related cortical excitability within motor areas and (2) that transient effects would be sustained as long as heart rate (HR) remained elevated. Subjects (n=23) were placed in a soundproof booth and instructed to perform a self-paced unimanual ballistic wrist extension every 3-6 seconds of the right wrist while holding a moveable handle. The motion involved a brisk contraction followed by relaxation and positional reset, collected continuously for approximately 8 minutes. Electroencephalography was used to measure movement-related cortical activity of the Bereitschaftspotential (BP) time-locked to onset of muscle activity associated with movement. The BP is a slow negative self-paced movement related cortical potential that precedes movement by approximately 1500ms. Current work commonly separates the BP into 3 main components early, late, and re-afferent Potentials. The early BP is representative of motor preparation of supplementary motor area (SMA) activity while the late component is representative of motor execution from primary motor cortex (M1). Early and late components are often distinguished by a a characteristic change in slope; where the early BP is a slow negative rise and the late components a steeper negative deflection beginning approximately 500ms prior to movement onset. Broken down further the late component consists of a portion of negative slope before giving rise to a peak approximately 100ms after movement onset known as the motor potential (MP). Following baseline measures, subjects performed 20 minutes of aerobic exercise at a moderate intensity (70% of age-predicted maximum heart rate) on a recumbent cycle ergometer. After the cessation of exercise, BP measures were recorded at two time points: immediately post-exercise (Post) and following a return to

baseline HR (Post[Rest]) and two additional measures separated by 15 minutes each (Post[Rest2] and Post[Rest3]) which was, on average, 45 minutes after the cessation of exercise. Electromyography (EMG) was employed over the extensor carpi radialis muscle belly to describe muscle burst activity and onset characteristics. Results determined that Early but not Late BP was influenced by aerobic exercise. This early movement related cortical adaptation is indicative of enhanced processing within supplementary motor area. Moreover, this effect was sustained for up to an hour and 15 minutes following exercise cessation. This data is suggestive that aerobic exercise influences on motor related cortical excitability is not driven by an aerobic exercise effect and is more indicative of a delayed neurotransmitter effect.

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List of Abbreviations

AE -	Aerobic Exercise
ATP -	Adenosine Triphosphate
BDNF -	Brain Derived Neurotrophic Factor
BG -	Basal Ganglia
BOLD -	Blood Oxygen Level Dependent
BG -	Basal Ganglia
CMA -	Cingulate Motor Area
CNV -	Contingent Negative Variation
CO_2 -	Carbon Dioxide
ECR -	Extensor Carpi Radialis
EEG -	Electroencephalography
EMG -	Electromyography
EOG -	Electrooculography
EPOC -	Excessive Post Oxygen Consumption
ERP -	Event Related Potential
gCBF -	Global Cerebral Blood Flow
GPi –	Globus Pallidus Internus
ICx -	Insular Cortex
IPAQ -	International Physical Activities Questionnaire
LTD -	Long Term Depression
LTP -	Lon Term Potentiation
M1 –	Primary Motor Cortex
MCA –	Middle Cerebral Artery
MRCP -	Movement Related Cortical Potential
NMDA -	*N*-Methyl-D-aspartate
PAR-Q -	Physical Activities Readiness Questionnaire
PEH -	Post Exercise Hypotension
PMCx -	Premotor Cortex
PMd -	Dorsal Premotor Cortex
PMv -	Ventral Premotor Cortex
PPCx -	Posterior Parietal Cortex
PVC -	Polyvinyl Chloride
RAP -	Reafferent Potential
RAH -	Reticular Activating Hypofrontality
rCBF -	Regional Cerebral Blood Flow
RP -	Readiness Potential
RPM -	Repetitions per Minute
SMA -	Supplementary Motor Area
SNr -	Substantia Nigra Pars Reticulata
VA -	Ventral Anterior Thalamic Nucleus
VL -	Ventral Lateral Thalamic Nucleus

CHAPTER 1: THESIS OVERVIEW

The primary objective of this thesis is to explore the influence that a single acute bout of aerobic exercise has on cortical excitability during simple movement production. The current literature in this area has focused mainly on examining the influence that exercise has on modulating cognitive markers in both healthy and patient populations. Accumulating findings over the past few decades provides convincing evidence in support for the use of aerobic exercise (AE) to enhance or prolong healthy cognition and/or prevent cognitive decline (Hillman, Erickson, & Kramer, 2008). Although these results are promising for cognitive research, currently a lack of literature exists on the influence that aerobic exercise may have on modulating the motor processing networks. The demand for research in this area stems from the increasing hypotheses that coupling aerobic exercise with traditional patient therapy sees measurable improvements in overall function, evident even in patients with motor impairment instead of cognitive impairment such as from a stroke (Quaney et al., 2009) and Parkinsonism (Bergen et al., 2002).

Although these studies have seen measurable improvements in behavioral outcome measures, no research known to date has attempted to explain the underlying neural mechanisms behind the recovery quantitatively. That being said, the influence that aerobic exercise has on cortical processing poses a unique and considerable challenge. Aerobic exercise of the lower-limbs such as walking, running and cycling produce a characteristic physiological response that globally affects healthy human cognition; evident in cognitive measures such as the P300 (Yagi et al., 1999). These global changes include alterations in cardiorespiratory and cardiovascular mechanics that appear to remain elevated even following exercise cessation (Maresh et al., 1992a). Even more interestingly, aerobic exercise appears to alter the neuronal environment post exercise, with measurable changes to blood biochemistry including increases in neurotrophins, neurotransmitters and energy availability (Chaouloff, 1989; Overgaard et al., 2012; Rasmussen et al., 2009). Due to the delayed nature of this response, some

individuals have proposed that it is this lasting change in environment that indirectly alters neuronal processing resulting in changes to cognition (Berchtold, Castello, & Cotman, 2010).

Young healthy adults were recruited to establish a relationship between aerobic exercise and movement related cortical excitability prior to movement execution. The current thesis required the use of electroencephalography allowing for a further understanding into how aerobic exercise may be influencing the underlying neural correlates of simple motor production. The use of young healthy adults will enable the investigation into the normal processing of the cortical regions involved. This empirical evidence will provide a preliminary framework and model for which further studies may be based. Furthermore, this thesis may establish a quantifiable measure to gauge motor cortical changes following aerobic exercise. This information in turn may be transferable and valuable to the understanding and plausible modification of current neurorehabilitative techniques.

CHAPTER 2: REVIEW OF RELEVANT LITERATURE

2.1 Primary Motor Cortex Organization

The Primary Motor Cortex (M1) is anatomically restricted to the pre-central gyrus and whose role is commonly associated with the mediation of movement. This area can be distinguished from other motor areas such as the supplementary motor area and premotor areas both cytoarchitecturally and by the decreased threshold required to elicit a motor response. For this reason the primary motor cortex is commonly defined as the region of the brain responsible for producing primary cortical efferent information that evokes voluntary movement (Penfield & Bouldrey, 1950).

Although the primary motor cortex can be referred to anatomically as the precentral gyrus, it is commonly referred in the literature cytoarchitecturally as either Brodmann Area 4 or agranular cortex and can functionally be broken down into many distinct regions, with considerable overlap (Sanes & Donoghue, 2011). Extended from work with non-human primates (Dum & Strick, 2002) and magnetic stimulation in humans (Metman et al.,1993), M1 follows a stereotypical topographic representation of the muscle groups it activates. This orderly parcellation progresses from hind limb medially, to forelimb and face laterally in non-human primates and similarly lower limb medially and upper limb and face laterally in humans.

Unlike the somatosensory cortex, whose representations is parceled into distinct smooth overlapping regions (dependent on the sensitivity or innervation density from lower regions), M1's representation appears to be less resolved and far more pixelated, coding for organized movements rather than individual muscle representations (Chouinard, 2006). Continual research in the area of micro and transcranial magnetic stimulation has provided insights into the substantial overlap that exists in the initiation of different movements (Wilson, Thickbroom, & Mastaglia, 1993). This has been confirmed

using intracortical recordings in monkeys which have shown that a single upper motor neuron has the capacity to activate a collection of lower motor neuron pools representing many individual muscles (Murray & Coulter, 2004).

Although the primary motor cortex can be stimulated to elicit a single muscle twitch using various techniques, it generally requires a vast array of input to achieve any meaningful volitional movement. Areas responsible for this are known as the secondary motor areas and have been discovered in non-human primates, with at least 5 separated distinct regions being shown to contribute (Chouinard, 2006). Specifically the regions of the Supplementary Motor Area (SMA), Ventral Premotor Cortex (PMv), Dorsal Premotor Cortex (PMd), Cingulate Motor Area (CMA) and Primary Somatosensory Areas 3a, 1 and 2 have been identified (Luppino & Rizzolatti, 2000). These regions contain a reciprocal connectivity with M1, and all contribute differently to the overall production of movement.

2.2 Pre-Movement Related Regions: Cortical & Sub-cortical

2.2.1 Supplementary Motor Area (SMA)

The supplementary motor area is found rostral to the primary motor cortex in the medial aspect of Brodmann area 6, and whose function has traditionally been coupled with the programming and coordination of complex movements. More importantly this area appears specialized for the production of self or internally generated movement, that is to say specified by internal rather than external cues. Remarkably, even imagined movement elicit similar Blood-Oxygen-Level-Dependent (BOLD) responses to similar actions being performed (Kim, Jennings, & Strupp, 1995), defining the preparatory motor role that the SMA plays in movement generation. The SMA has since been subdivided into the SMA proper (caudal SMA) and the pre-SMA (rostral SMA), which lies immediately anterior to it. Major deficits appear in monkeys affected by lesions to the SMA including a reduction in spontaneous movements, the inability to orient hands and digits appropriately during reach to grasp and the inability to coordinate

bimanual hand movements (Brinkman, 1984). Interestingly enough, the ability for SMA lesion patients to react to externally cued movements remains relatively intact (Brinkman, 1984). This suggests that the SMA typically draws from a pool of motor sequences from memory, rather than relying on reaction to a peripheral stimulus.

Research in the past few decades has suggested that a considerable overlap of direct connections exists between the SMA and M1 within the spinal cord (Dum & Strick, 2002). However, movements elicited by stimulating the SMA require more intense and longer-lasting trains of pulses than do movements evoked from the primary motor cortex (Maier et al., 2002). This response is directly related to the strength of connection at the spinal cord level. In most cases it appears that the direct projections from M1 result in a larger concentration of monosynaptic connectivity then from SMA projections (Maier et al., 2002). These direct projections appear important in mediating movements involving proximal muscle while the SMA indirectly influences the more distal muscles via vast cortico-cortical connections to both ipsilateral and contralateral M1's (Tanji, 1994). Another interesting characteristic of SMA activation is that it is typically recruited during bilateral movements, most likely due to the vast interconnectedness via the corpus callosum (Rouiller et al., 1994).

As noted above, the SMA is commonly divided into two parts; SMA proper and pre-SMA (Macpherson et al, 1982; Matsuzaka, Aizawa, & Tanji, 1992). The primary cortical input to the SMA proper (within the macaque cortex) is the "supplementary sensory area" or parietal area of the caudal cingulate sulcus, an area highly correlated to the primary and secondary somatosensory areas within human cortex (Rizzolatti, Luppino, & Matelli, 1998). The SMA proper also shares vast connections with the pre-supplementary motor area (pre-SMA) which is believed to produce a sequential pattern of activation related to movement generation (Ikeda et al., 1992). Unlike the SMA proper whose primary role in movement is the setting of simple motor programs from memory, the pre-SMA is typically active

during learning of new complex motor programs (Akkal et al., 2002; Nakamura, Sakai, & Hikosaka, 1998; Sakai et al., 1999). For this reasons, the pre-SMA shares a cluster of connections with frontal regions such as the PMd, PMv, M1, CMA and other regions such as the basal ganglia (BG) and posterior parietal cortex (PPCx) (Luppino & Rizzolatti, 2000; Picard & Strick, 1996). However, once a motor skill is practiced and refined, a preferential shift from pre-SMA to SMA proper takes place, with the final lag of motor skills (automaticity) shifting directly to M1.

The role that the two SMA components contribute to movement generation produces a stereotypical temporal activation pattern (Nakamura et al., 1998). More specifically, movement related discharge of SMA cortical neurons begins to occur approximately one second before the onset of movement (Barrett, Shibasaki, & Neshige, 1986). These potentials measured by either intracortical or electroencephalography (EEG) recordings, producing a characteristic negative potential know as either the Bereitschaftspotential or readiness potential (Refer to 1.3.1) (Dirnberger et al., 1998). All in all the contribution from the SMA appears to be intimately involved in the selection of behaviorally relevant voluntary motor actions.

2.2.2 Premotor Area

A region found just rostral to the precentral gyrus which incorporates the lateral constituent of Brodmann area 6. Similarly to the anatomical structure of the SMA, the Premotor Cortex (PMCx) contains two components Dorsal Premotor Cortex (PMd) and Ventral Premotor Cortex (PMv) (Shibasaki & Hallett, 2006). In addition the PMCx contributes both directly to descending fibres, particularly the reticulospinal tract and to regions of the spinal cord responsible for proximal and axial muscles as well as reciprocal projections to M1 (Hoshi & Tanji, 2007; Luppino & Rizzolatti, 2000). The significance of these contributions provides insight into the functional ability of the PMCx to control initial phases of orienting the body and arm to a target based on sensory information. Unlike the SMA, the PMCx often relies on

external indicators such as visual or somatosensory cues which signify a particular action is required or will be required in the near future. For this reasons the premotor cortex is heavily connected with sensory integration centres such as the posterior parietal cortex (PPCx) (Chouinard, 2006; Wise, 1985). Individuals suffering from lesions to PMCx have difficulty in responding to cued stimuli and proper selection of movements even when instructed and capable of performing actions.

Finally, much like SMA activity to be primarily associated with Bereitschaftspotential production, the PMCx's activity is associated as the greatest contributor to a similar scalp recorded potential known as the Contingent Negative Variation (CNV) or the even more closely related cued movement related potential which is time locked to movement onset. . Although the characteristic morphology of the Bereitschaftspotential, CNV and cued-MRP's are similar (slow negative potentials), they represent two very different aspects of movement production. These three potentials share a common temporal movement related discharge occurring 1-2 seconds before movement, however are measured using different onsets. Kornhuber and Deecke's Bereitschaftspotential and cued-MRP's are time locked to the onset of movement, while the CNV is time locked to a stimulus. Interestingly, cued MRP's appear to follow nearly identical pattern generation to that of the BP developing the same main 3 components (Early, Late, and Reafferent), however the generators are different (Smith et al., 2012). As previously mentioned the early BP is generated within the SMA followed by a preferential switch to M1 activity representative of a late BP component. In the same way the cued MRP is generated within PMCx during the early component and switches to late component M1 activity. The main difference is during the initial stages, where the BP is self-generated the cued-MRP relies on external sensory triggers to initiate motor preparation. For this reason cued-MRPs are not typically maximal over central sites (FCz or Cz) like the BP but are appear in the more biased to contralateral sites of the future movement. The diverse contributions that these different cortical regions provide to the production of movement, produces the

ability for the interaction between nervous system and the surrounding environment; whether it be intrinsically driven (SMA) or in response to extrinsic stimuli (PMCx).

2.2.3 Basal Ganglia

The basal ganglia are a collection of 5 subcortical nuclei highly involved in the production and control of movement. Although the basal ganglia contain a vast interconnectedness with other motor centres of the cortex, they do not directly contribute to any motor tracts of the spinal cord. The five interconnected nuclei of the basal ganglia are: the caudate nucleus, globus pallidus, putamen, substantia nigra, and subthalamic nucleus. Functionally some of these nuclei are grouped as the striatum (caudate and putamen) and the pallidum (globus pallidus and substantia nigra pars reticulata). These subcortical nuclei are responsible for input/output loops involving the motor cortex via the ventral anterior (VA) and ventral lateral (VL) thalamic nuclear complex.

The neurons that contribute to these loops modulate their own activity and are responsible for the normal production of volitional movements through parallel facilitatory and inhibitory pathways. This is achieved by anticipating and online monitoring of the initiation and continuation of movement. The primary input to the basal ganglia has origins from almost all areas of the cortex via the corticostriatal pathway; frontal and parietal lobes being the largest contributors with less but still substantial contributions from temporal and cingulate cortices.

The principal output from the basal ganglia back to the cortex occurs via the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr); high frequency tonic inhibitory outputs. The coordinated calibration between inhibitory and excitatory input to these nuclei result in varying levels of suppression of the VA/VL nuclear complex. That is to say, the input to the GPi and SNr is either inhibitory or excitatory resulting in enhanced suppression or disinhibition. The VA/VL and cortex make up a major thalamocortical pathway that contributes to almost all voluntary motor control. Due to this intimate

relationship between the basal ganglia, supplementary motor areas and primary motor cortex, it can sometimes be difficult to disentangle their individual contributions to overall movement production.

2.3 Movement Related Cortical Potentials

2.3.1 Bereitschaftspotential

First discovered nearly 5 decades ago by Kornhuber and Deecke (Deecke et al., 1976) the Bereitschaftspotential (BP) is a slow negative wave that precedes self-paced voluntary movement. Synonymous with the readiness potential (RP), the BP is an event related potential (ERP) that is recorded through the use of electroencephalography (EEG) and is commonly separated into two phases (Kornhuber & Deecke, 1965). BP's have been recorded prior to finger, hand, wrist, foot, saccadic eye movements, and before speech production. The BP has an amplitude ranging from 1 to 10 μV and can be resolved through averaging 50-100 artifact free trials given that the averaging period is sufficiently long: 3-5 seconds (Shibasaki & Hallett, 2006). The most practical physiological generation for the Bereitschaftspotential is a summation of excitatory postsynaptic potentials from the apical cortical dendrites (Colebatch, 2007). An important first step in identifying the generators of the BP may be clarification of the specific motor, cognitive and motivational processes that contribute to its genesis.

As previously stated it is common to separate the BP into two different phases. The early phase or BP1 begins about 1.5 to 2 seconds before muscle onset and is represented by a slowly rising negative potential. On the other hand the late phase or BP2 begins about 500 ms before muscle onset and is dissimilar from the early phase by its distinct increase in slope of negativity (Shibasaki & Hallett, 2006). This state is followed by two more components that are commonly explicit in the literature; they are the peak BP which has a latency around 70-160 ms after movement onset and the re-afferent potential (RP) with a latency between 200-350 ms post movement (Colebach, 2007). That being said, in some individuals it can be difficult to distinguish between the two pre-movement phases as the literature has

yet to agree on criterion for each phase (Barrett et al., 1986). However, according to Shibasaki and Hallett (Skibasaki and Hallett, 2006) it is important to separate these phases when possible as they appear to have separate generators.

One hypothesis for instance states that the early BP appears to reflect activity from populations within the SMA, which evidence supports from both dipole source analysis (Praamstra, Stegeman, & Horstink, 1996) and fMRI models (Cui et al., 1999). In addition, the late BP emerges from an additional activity contribution from contralateral M1. This suggests that a temporal sequence in brain processing that produces the subjects "intention" to act (Cunnington et al., 2003). The early BP has been observed to have symmetrically characteristics distributed between the two hemispheres seen by its maximum amplitude in frontal midline electrode sites (FCZ,CZ), becoming more lateralized (contralateral) during later phases (Libet, Gleason, & Wright, 1983; Matsuhashi & Hallett, 2008). Some have noted that the BP components are usually unclear in individual data, but appear clearer in grouped averages.

Moreover, the early BP is not essential, at least for simple movements, and consists in part of non-specific "preparation" for movement, such as facilitation of cortical and subcortical motor pathways. Projections by way of the basal ganglia and thalamus most likely underlie the switching between areas of cortical activation and the phases of the BP. The late BP most likely represents a period of intense interaction between SMA proper and motor cortex during which selection of appropriate muscles for activation occurs. For these reasons, many different factors are able to alter the production of the BP in surface recordings. Some evidence supports that changes to muscle selection, force and speed of contraction can affect the presentation of the BP (Barrett & Shibasaki, 1986; Deecke, Heise, & Kornhuber, 1984). On the other hand, task manipulations such as movement complexity (Shibasaki & Hallett, 2006), preparatory state (Leuthold & Schröter, 2011), and the addition of motor learning (Loveless, 1974) have been shown to modify the appearance of the BP. Finally within disease

states such as Parkinsonism (Hatta et al., 2009; Margo Taylor, 1978b), Dystonic (Dick et al., 1989), Praxis (Van der Kamp et al., 1995) and cerebellar lesion patients (Wheaton, Yakota, & Hallett, 2005) appear to have some alterations in the production of the BP, whether it is amplitude or onset. The data from these models provide unique insights into how different anatomical and functional pathways contribute to the overall generation of the BP. In particular, Parkinsonian patients present with a diminished or non-existent early BP, while the late BP remains relatively intact (following movement generation) (Dick et al, 1989). This information provides a basis for the inclusion of the basal ganglia as a contributor, whether indirectly, to production of the early BP but not the late. Due to the dense connectivity between the basal ganglia and SMA, this hypothesis would not be unreasonable.

Although it is not well understood what function the slow negative potentials represent, what is agreed upon is that the BP appears to be a measure of a prepared or readiness state for subsequent motor action (Kitamura, Shabasaki, & Terashi, 1999). Based on the evidence of the sensitivity of the BP to mechanical load and task difficulty, it can be assumed that the BP also reflects the degree of effort associated with the movement. Moreover, it is possible that the different BP generators contribute separate cognitive, motivational and motor processes to the overall generation. That is to say, while the secondary motor areas (SMA/cingulate motor area) engage to select, time and initiate action, the primary motor regions (SMA proper/motor cortex) are more directed towards movement execution (Shibasaki & Hallett, 2006). Furthermore, evidence supports that numerous intracortical generators exist including the basal ganglia and thalamic nuclei (Stephan et al., 1995), which is not surprisingly due to the nature of these nuclei to regulate motor cortical excitability activation and movement initiation.

2.3.1.1 Factors Influencing Bereitschaftspotential Morphology

As noted above, the nature of BP generation makes it susceptible to many different factors that appear to influence it's morphology including its magnitude and time course. Typical behavioral

manipulations include level of one's intention to move, how prepared they are to move and the ability to freely select movement versus fixed movement selection. The movement itself is a strong mediator of BP appearance, with force exerted, speed, and precision of the movement providing numerous variations. Finally, the discreteness and complexity of movement, along with the level of learning and skill acquisition associated with the movement produces a number of unique BP profiles. Specifically, the speed and force of movement that generates the BP appears to influence the early BP profile; proportionate increases in speed and force increases latency and amplitude respectively (Shibasaki & Hallet, 2006). However, as the complexity, precision and level of skill increases the late BP morphology favors an increase in peak BP amplitude with no influence appearing in early BP (Shibasaki & Hallett, 2006).

2.3.2 Other Event Related Potentials (N30)

In addition to the motor related cortical potentials (MRCPs), other event related potentials (ERPs) commonly associated with cognitive or somatosensory processing are prominent in the literature. One common method for evoking these potentials is through the use of electrical stimulation of peripheral nerves; such as the median nerve, which produces a high quality signal to noise ratio (Leuthold & Jentzsch, 2001). These electrical stimuli recruit a bundle of peripheral nerve fibres that produce a collective volley of muscle, joint, skin and deep tissue information. This volley enlists sensory neurons from the peripheral nerve, spinal cord and cortical neurons that results in a stereotypical serial representation of positive and negative deflections in EEG recordings (Vallbo et al., 1979). Interpretation of these profiles can provide useful information into how the underlying afferent systems may be influenced by either internal or external conditions or treatments.

Short latency cortical SEPs commonly occur in the latency range of 20-40ms and can be distinguished by frontal (P20 and N30), central (P25 and N35), and posterior (N20 and P30) sites (Allison

et al., 1991). Once believed to represent similar depictions of the same generators, recent literature has challenged this, with some arguing very different and unique generators (Balzamo et al., 2004). The N30 component site of origin still remains subject to debate thought by some to be generated within SMA (Barba et al., 2005) some data suggest possible mediation by M1 activity (Shimazu et al, 1999). What is agreed upon is that the N30 is clearly influenced by motor behaviour, and in most studies it is decreased in amplitude in patients with Parkinson's disease similar to that of the BP (Babiloni et al, 1994; Barba et al., 2005; Brown, 2011). When implanted electrodes of the globus pallidus internus or subthalamic nucleus are stimulated, a distinct return of the N30 occurs in scalp recordings, while the central or posterior potentials listed above remain unchanged (Boecker et al., 1999). Based on the understanding of the intimate relationship between the basal ganglia and SMA, it can be proposed that the N30 is produced bilaterally in the SMA and modulated through a bottom-up mechanism via the basal ganglia.

2.4 Aerobic Exercise

2.4.1 Acute Physiological changes from resting state to recovery

With increasing support for the implementation of exercise in special populations many researchers have turned to looking at the global effects it may have on healthy populations. Exercise appears to provide improvements to a number of aspects on cardiorespiratory, cardiovascular and neural physiology (Morris & Hardman, 1997; Hillman et al, 2008).

During an acute bout of aerobic exercise, metabolic demand within participating muscles drastically increases. As the concentration of adenosine triphosphate (ATP) is depleted by continuous muscle contraction, numerous other biochemical, thermal and physiological responses begin to take place. Allocation of additional resources required by muscles is achieved through increases in glucose, oxygen and fat metabolism, followed by the removal of increasing levels of carbon dioxide (CO_2). Resource mobilization during exercise is largely driven by drastic increases in plasma concentration of

hormones such as cortisol, insulin, glucagon and catecholamines (epinephrine and norepinephrine)(Evans & Cyr-Campbell, 1997; Warburton & Nicol, 2006). Consequently, as the demand by the muscles increases and immediate supply diminishes, additional compensatory mechanisms are enlisted. A tight coupling of both respiratory and cardiovascular changes respond to increasing levels of CO_2, and oxygen deficit (Galbo et al., 1977). This response is followed by a relatively rapid adjustment to heart rate and contractility producing larger cardiac outputs, consequentially providing a greater supply to muscles. Finally, a redistribution of blood flow during exercise occurs from a synergistic combination of vasodilation within participating muscles and vasoconstriction in other tissue, with only one exception to this global behavior; the brain.

Following cessation of exercise, metabolism remains elevated for several minutes, the magnitude and duration of this effect is directly related to the intensity level of the exercise (Cummin et al., 1986). Theories behind why excess post-exercise oxygen consumption (EPOC) remains elevated post-exercise are threefold. (1)During acute bouts of moderate to intense exercise, a larger component of creatine phosphate is consumed; this system requires oxygen in order to restore creatine phosphate to resting levels (Gore & Withers, 1990). (2)Due to the lag in resource allocation to muscle, a period of time exist when the muscles are oxygen deprived, this increases the production of lactic acid or lactate, which muscles remove via the cardiovascular system and delivered to the liver. Inside the liver the cori-cycle breaks down lactate into oxidized pyruvic acid, glucose and amino acids. In reality, the concentration obtained during exercise overwhelms the cori-cycle producing a delayed lactic acid removal, thus an extended time period exists when plasma lactate levels remain high. For example, young healthy individuals who exercised at a moderate intensity (60% VO_2 Max) saw elevated levels of serum lactate for up to 40 minutes post exercise (Maresh et al, 1992). These results are significant due to the fact that the cori-cycle relies heavily on a constant demand for oxygen, therefore contributing to the EPOC (Maresh et al., 1992). (3) Finally heart rate and ventilation remain elevated requiring a residual amount

of oxygen following aerobic exercise; this is mainly due to accumulation of $PaCO_2$ during the course of exercise (Barnard & Foss, 1970). Eventually the above processes will return to a resting equilibrium, however the lag period in which this occurs is based on one's individual adaptations and fitness level (Maresh et al., 1992).

Aforementioned particular substrates are drastically increased during aerobic exercise and sustained through the EPOC period; one of which is lactate. Commonly regarded as a waste product in muscles, reports have shown that lactate is an important molecule in healthy neuron metabolism (Da Sedlock, 1997). The hyperlactemia that occurs during the first few minutes of EPOC following moderate to intense prolonged aerobic exercises is subsequently followed by increases in uptake of lactate by the brain (Bouzier-Sore et al., 2003; Ide et al., 1999; Wyss et al., 2011). This increase in substrate availability during maximal aerobic exercise reduces the cerebral metabolic ratio by 30-40% (Da Sedlock, 1997; Schurr, 2005). Dalsgaard et al. (2003) has proposed that the reduction in cerebral metabolic ratio that continues after exercise is a direct result of a continual influx of lactate and glucose that is metabolized into other molecules such as neurotransmitters or oxidized at a later time period (excess of 40 min post exercise).

However, the authors concluded that lactate does not appear to be accumulated and stored, instead, only replenished. This data suggest a possible mechanism by which aerobic exercise may provide a basis for the augmentation of cortical excitability in the first short periods following exercise. For example, if regional cortical activity were to increase during the EPOC period, an additional resource would be available allowing those active neurons to become more efficient then they would be at rest. Interestingly some data does support that following exhaustive exercise that results in a drastic increase in lactate, an increase to motor cortical excitability occurs as evaluated by transcranial magnetic

stimulation (Coco et al., 2010). This shows neuronal activity may be altered by the energy source available within the circulating blood stream following exercise.

2.4.2 Acute Adaptations to Cerebrovascular Dynamics During and After Aerobic Exercise

As mentioned above, global brain blood flow (gCBF) remains relatively constant between both rest and exercise states. This general rule developed by Kety and Schmidt (Kety & Schmidt, 1945) holds true as long as blood pressure (60-150 mmHg) and arterial CO_2 pressure levels remain within the ability of cerebral autoregulation. Therefore gCBF perfusion does not increase in response to increases in either $PaCO_2$ or blood pressure (Kety & Schmidt, 1945), but instead is coupled to neuronal metabolic demand. Thus while gCBF is maintained, regional perfusion can substantially change, which appears to be limited to discrete pockets of active neuron populations, including motor and sensory areas. Dynamic exercise has been shown to elevate regional blood flow to SMA and primary sensorimotor areas (Madsen et al., 1993). These active changes appear to be specific to each hemisphere, with Linkis et al (Linkis et al., 2002) demonstrating a large mean velocity change (+19%) in left middle cerebral artery (MCA) during a right-handed contraction task, compared to right MCA (+4%).

However, following the cessation of an acute bout of moderate to intense aerobic exercise, cerebrovascular dynamics can be altered for substantial length of time (Linkis et al., 2002). A well-documented phenomenon known as “Post Exercise Hypotension” or PEH has gained support in recent years (Forjaz et al., 1998). Like resting hypotension, PEH is characterized by a consistent drop in systemic vascular resistance resulting in a systematic drop of approximately 10mmHg in normotensive individuals. Although findings for PEH in normotensive human subjects has been shown inconsistently, pre-hypertensive and hypertensive individuals have shown consistent PEH differences (Halliwill, 2001; MacDonald, 2002; Williamson, 2004). The modulation of vascular dynamics appears to begin shortly after exercise cessation and continue for up to 12 hours in some hypertensive individuals; less for

normotensive on the order of 7-8 hours (Kenney & Seals, 1993). Despite the fact that many hypotheses exist that attempt to explain the mechanisms of PEH including sustained sympathetic inhibition (MacDonald, 2002), vasodilator concentration (Kulics, Collins, & DiCarlo, 1999) and increased modulation in specialized baroreceptor nerve populations (Collins, Rodenbaugh, & DiCarlo, 2001), no one theory has emerged triumphantly (Chen & Bonham, 2010). Important to note is the dependency to type, duration and intensity of exercising has on the ability for PEH to alter vascular behavior (Halliwill, 2001).

Emerging evidence supports that PEH produces differences in regional cerebral blood flow (rCBF) patterns compared to resting states (MacDonald, 2002). Following the termination of exercise, PEH appears to influence cerebral regions that are intimately involved throughout the course of exercise. First, areas involved in autonomic regulation of blood pressure including bilateral insular cortices (ICx) have been shown to have a substantial decrease in rCBF, which some believe may be a driving force behind PEH (Lamb et al., 2007; Williamson McColl, & Mathews, 2004). Similar regional changes have also been shown within the sensorimotor cortices responsible for muscles involved during the exercise (Williamson, McColl, & Mathews 2004). Moreover others have shown that 30 minutes post cycling of the lower limbs, total gCBF remains elevated (20% increase compared to pre-exercise) for up to 30 minutes mirroring significant reductions in systolic blood pressure (Smith et al., 2010). Furthermore, Smith et al. (2010) suggested that an acute bout of aerobic exercise retains in some aspects, an ability to enhance rCBF at the 30 minute post exercise time point during a repetitive finger tapping task. However, the authors did caution any inferences that the changes due to aerobic exercise could have on changes to underlying neuronal activity.

All in all, cerebrovascular changes during and post exercise are intimately coupled to neuronal behavior (Lamb et al., 2007). Exercise appears to have a profound influence on regions involved in the

generation of exercise with transient changes in rCBF. Interestingly this influence is able to translate to non-exercising muscle groups (upper limb), with pronounced results with sustained drops in systemic blood pressure or post exercise hypotension.

2.4.3 Influence on Cognition and Overall Neurological health

With regards to the nervous system, healthy participants who undergo regular aerobic exercise are subject to a beneficial improvement in neural processing via direct and indirect pathways; whether one or the other has more of an effect is still unclear. Directly, exercise requires the recruitment and synergy of specific neural systems such as the motor cortex, basal ganglia and cerebellum, in order to allow the body to perform any form of exercise. Indirectly, exercise consequentially leads to changes in hormonal, immune, and vascular responses that may also influence various areas of the brain (Pedersen et al, 2000; Ide & Secher, 2000).

One subset of processes responsible for online adjustments to perception and biasing of contextual information is known as cognitive control. In other words, cognition is the process by which information is gathered and interpreted for a goal oriented response. One common measure of cognition is the electroencephalography potential the P300 (Raz, 2005). Although the exact generators that mediate the P300 response is yet unknown, its response appears concentrated within the frontal lobe (Polich & Kok, 1995). Currently, an abundance of literary evidence supports that aerobic fitness provides benefits to cognition in all aspects structure and function (Linden, 2005); from cell to behavioural level. In addition, research has shown that continual aerobic exercise training can result in improvements in cardiorespiratory control subsequently followed by increases in cognitive performance, reducing the diminishing effects of healthy aging (Hillman et al., 2008; Hillman, Snook, & Jerome, 2003; Rhyu et al., 2010; Voss et al., 2011). This is represented by a significant decrease in P300 latency and increased P300 amplitude (Colcombe et al., 2003). Furthermore, single bouts of acute

aerobic exercise at moderate intensity still appear to elicit short term cognitive benefits, similar to those of trained individuals (Dustman et al., 1990). All in all, physical activity, more importantly aerobic fitness appears to be a strong mediator of cognitive health in healthy populations (Chang et al., 2012).

One proposed mechanism for how aerobic exercise training may be causing these improvements in cognition is through enhancements in neuro-plastic properties, predominately capacity for long term potentiation (LTP), long term depression (LTD) and eventual synaptogenesis. One molecule in particular that is utilized during the development of LTP and whose transcription and release is susceptible to modulation by exercise is known as brain derived neurotropic factor (BDNF) (Barnes et al., 2003). Early phases of LTP are a result of close temporal summations of pre and post-synaptic activity that is associated with an increase in N-methyl-D-aspartic acid (NMDA) receptor activation and calcium signaling (Gomez-Pinilla, 2002; Rasmussen et al., 2009; Vaynman, Ying, & Gomez-Pinilla, 2003). Generally, acute changes to local BDNF concentration levels appear to alter, in the short term, the sensitivity of pyramidal and interneuron cell cultures to both excitation and inhibition (Desai, Rutherford, and Turrigiano, 1999). Furthermore, sustained BDNF concentration has been shown to have a stabilizing effect on existing synapses while allowing for the augmentation of synaptic terminals, and induction of additional dendritic outgrowths (Kovalchuk et al., 2002). Even single bouts of moderate and high intensity aerobic exercise have been shown to increase circulating BDNF levels in humans (Levine et al., 1995), furthermore these circulating BDNF levels support brain plasticity (Rasmussen et al., 2009). One important aspect of BDNF is that its neuronal uptake is related to level of activity, in other words cells that are more active typically increase both their uptake and transcription of BDNF (Berchtold et al., 2010). Therefore, these short and long adaptations to neuronal behavior, driven in part by increases in BDNF concentration following aerobic exercise, provide one aspect by which aerobic exercise may modulate cortical excitability in vivo.

CHAPTER 3: RESEARCH OBJECTIVES AND HYPOTHESIS

The principle goal of this thesis is to provide insights into the role that an acute bout of aerobic exercise has on altering cortical contributions to motor preparation and execution. As noted above, aerobic exercise appears to retain a unique ability to alter many aspects of the neuronal environment, which may in turn lead to alterations in neuronal behavior. This thesis hopes to distinguish which cortical areas used during self-generated movement are the most susceptible to modulation. This modulation will be quantified by the subtle changes that appear in event-related potentials, more specifically the Bereitschaftspotential and the N30. Understanding the interaction that treatment of even a single bout of aerobic exercise has on modulating movement-related cortical potentials provides further evidence to support current models describing the influence of acute aerobic exercise on the brain. Therefore the main objectives of the current research are as follows:

(1) To determine if an interaction exists between a single bout of aerobic exercise and the cortical areas involved in simple motor production.

    Hypothesis: Cortical excitability will be transiently enhanced following aerobic exercise cessation. This will manifest as alterations in the morphology of the Bereitschaftspotential production especially changes to early and late BP will establish that aerobic exercise does in fact alter motor cortical areas.

(2) To determine and characterize the transience and attributes of such an effect on motor cortical areas, especially in the time periods following exercise cessation.

    Hypothesis: Following exercise cessation, the transient enhancement to motor cortical excitability will remain elevated and will progressively return to pre-exercise values mirroring other physiological measures such as heart rate.

(3) To determine how diffuse the influence of aerobic exercise is to altering the cortical response to both the production and interpretation of motor (BP) and motor produced sensory information (N30).

Hypothesis: Following exercise cessation, an enhancement in the N30 event related potential both in onset and amplitude will occur; this enhancement will mirror the effects seen in the Bereitschaftspotential.

CHAPTER 4: INFLUENCE OF AN ACUTE BOUT OF AEROBIC EXERCISE ON BEREITSCHAFTSPOTENTIAL ELICITED FROM A BALLISTIC WRIST EXTENSION IN HEALTHY INDIVIDUALS

4.1 Introduction

An increasing amount of evidence supports the use of physical activity for modifying brain activity. Specifically, higher fit individuals appear to be the beneficiaries of several health and cognitive improvements; especially with regards to aging (Kramer et al, 2006). More recent evidence lends support that even single bouts of aerobic exercise have been shown to improve later cortical processing in young healthy participants (Hillman et al., 2008; Rhyu et al., 2010; Voss et al., 2011). With regards to cognition this often translates behaviorally to improvements to speed and not accuracy of responses to choice speeded reactions (McMorris et al, 2011). The authors hypothesized that short term improvements in speed are representative of a facilitation effect on neuron processing while the lack of influence on accuracy is directly related to its requirement for enhanced synaptic plasticity. Through the course of a speeded reaction, 4 major cortical processes are undertaken; stimulus detection, stimulus evaluation, motor preparation and execution. Historically one event related potential known as the P300 has been employed to assess the influence of aerobic exercise on cognition or the stimulus evaluation phase of a response and is responsible for the categorization of the stimulus in order to produce a correct goal driven response. Recent findings have shown that aerobic exercise enhances the morphology of the P300 in both its amplitude and latency (Hillman et al, 2003, Kamijo et al, 2004a). Moreover, some researchers attribute the enhancement to speeded choice reaction times on this augmentation within the P300. However the P300 only reflects one component of the overall cortical processes that generated the response, therefore it is possible that the enhancement to speeded choice reactions could be driven by a combination of both cognitive and motor states.

Preliminary work using the Contingent Negative Variation (CNV) has shown that moderate aerobic exercise influences both early and late CNV amplitudes similar to that of the P300 (Kamijo et al, 2004b). The CNV is a negative potential that develops in the time period between a warning and go stimulus and is thought to reflect both cognitive (Early CNV) and motor preparation (Late CNV) states. This data suggest that there is an enhancement to motor preparation following acute bouts of moderately intense aerobic exercise. However, the interpretation of the late CNV generation is still somewhat controversial with some evidence in support for a cognitive contribution and other support for its motor preparation properties (Rohrbaugh & Gaillard, 1983; Brunia, 1999); what has been shown is that the CNV is not contingent on a motor response (Donchin et al., 1973). However when a motor response is produce, additional research lends support to its possible motor preparatory properties due to its likeness to another event related potential known as the Bereitschaftspotential or Readiness Potential (Grunewald et al., 1978). In an attempt to decipher the influence that aerobic exercise has on the cortical contributions to motor preparation and execution in the absence of cognitive contributions the Bereitschaftspotential was employed in the current study.

Since its discovery nearly 35 years ago by Deecke and Kornhuber (Deecke and Kornhuber, 1976), the internally generated Bereitschaftspotential has been used as a marker for assessing many different neurological processes including motor preparation and execution. The Bereitschaftspotential is a movement related potential that supersedes motor production by approximately 1500ms. Although previous authors have concentrated on viewing the BP as a single amplitude measure (Kornhuber & Deecke, 1965), further investigation with the Bereitschaftspotential suggested that it may be more informative to measure the BP based on its two distinct gradients (Deecke et al., 1976; 1984;Deecke et al., 1987; Taylor, 1978a). The BP is commonly broken down into two main components, referred to as early and late BP; distinguished by their characteristic changing slopes and named by their sequential distribution (Colebatch, 2007; Shibasaki & Hallett, 2006). The early BP has traditionally been associated

with the activity of the supplementary motor area, and represents early motor planning and selection (Shibasaki & Hallett, 2006). On the other hand the late BP is associated more with primary motor cortex and represents a shift from early movement preparation to motor production (Cui et al., 1999; Ikeda et al., 1992). The latency and morphology of these potentials is heavily related on the attributes of the movement itself, with force, velocity and precision of movement influencing both BP components differently (Colebatch, 2007).

Currently a lack of research exists on the investigation into the influence that acute bouts of aerobic exercise has on motor related cortical potentials. However, in an attempt to understand the possible underlying neurophysiology combined with exercise, we must first understand current proposed mechanisms on cognition. Although many have investigated the exercise-induced effect on cortical processing, only few have attempted to decipher the underlying mechanisms of its influence. Currently a general framework has begun to develop in an attempt to explain how acute bouts of aerobic exercise may drive changes in cortical processing. The first proposed mechanism was developed by Davey (1973), who witnessed enhancements and detriments in mental performance following moderately intense and severe physical exertion respectively. Davey hypothesized that this inverted-U relationship was a result of changes in arousal state between the two exercising states. Building on this Cooper (1973) proposed that increases in afferent information during exercise lead to greater activity within the reticular formation; this in turn produces a greater increase in central catecholamine release resulting in an elevated state of arousal.

More recent literature has expanded the knowledge of the reticular activating formation and it is now considered to be a component of an overall reticular activating system containing many different but interrelated arousal systems. Based on this knowledge combined with the assumption that cognition is separated into implicit and explicit domains, Dietrich and Audiffren (Dietrich & Audiffren, 2011) developed a general model of how acute aerobic exercise influences mental performance. According to

the model aerobic exercise enhances both the activation of the reticular activating process and disengagement of the explicit cognitive system from hindering the current cognitive task; both of these combined, aim to facilitate implicit knowledge and overall enhance outcome measures. The model was therefore named the reticular activating hypofrontality (RAH) because it involves an enhancement to the reticular activating process and a suppression of prefrontal regions responsible for higher order explicit knowledge. Therefore this model when combined with emerging evidence supporting increases in central catecholamines release during exercise, we begin to develop an understanding of the exercise-induced effect on cognition. Based on the fact that aerobic exercise appears selective to speed rather than accuracy and it is assumed that the reticular activating hypofrontality enhances implicit knowledge to which motor information is most commonly associated, it is proposed that similar mechanisms will drive the changes in movement related cortical potentials.

Therefore the purpose of the current study was two-fold; first to determine whether or not an acute bout of aerobic exercise contains the ability to modulate cortical excitability within the areas that are responsible for the production of movement. Second, this study investigated the time course that such effects may take place with relation to physiological measures such as heart rate. Based on current cognitive work it is hypothesized that aerobic exercise will: (1) influence movement related cortical potentials similar to those seen in cognitive markers (P300 & CNV) and (2) be elevated for a short period of time following aerobic exercise.

4.2 Materials and Methods

4.2.1 Subjects

Twenty three healthy volunteers were tested (Study A: 6 Males, 5 Females; age range 22 to 38 years; average 27.09 years; Study B: 6 Males, 6 Females; age range 20 to 31 years; average 24.72 years). Exclusion criteria were the ability to perform an acute bout of aerobic exercise on a recumbent cycle

ergometer and successfully complete the Physical Activity Readiness Questionnaire (PAR-Q). In addition individuals could not be receiving treatment (and have no history of being treated) for a major neurological illness or event such as seizures/concussion. Experimental procedures were approved by the Office of Research Ethics at the University of Waterloo, all subjects gave their informed consent to participate in the study and when necessary participants received compensation at a rate of $10/hour. All participants for study B were collected at 1300 hour and instructed to have breakfast the morning of the test. All in all of the twenty three participants only two participants were excluded from data analysis for study 2. One participant was unable to complete aerobic exercise at the set intensity and therefore was unable to be included in data analysis. Furthermore, one participant was removed from Bereitschaftspotential analysis as a result of lack of epochs from excessive blink artifacts. Therefore 21 participants in total were included in the analysis across studies A (11 subjects) and B (10 subjects).

4.2.2. Experimental Procedure

Baseline Physiological Testing

Participants resting heart rate was measured using a Polar™ wristwatch-to-chest monitor; these measures were taken prior to, immediately after exercise and continually every 3 minutes until heart rate returned to rest. After completing the motor task immediately after exercise, they were also monitored until they return to pre-exercise values before beginning the final testing block. Study B included an additional blood pressure measurement through the use of a stethoscope and pressure cuff; blood pressure was taken immediately following heart rate values.

Apparatus

Two different hand apparatuses were used between the two study components. Study A involved the use of a custom designed apparatus consisted of a Polyvinyl Chloride (PVC) handle attached

to a plexiglass platform with an imbedded potentiometer at the base of the handle (Refer to Appendix Figure 1). Study B consisted of an apparatus with an elevated metal handle that was fastened to the table. The hand was secured to the handle using a Velcro™ hand strap that restricted motion of the hand to flexion and extension of the wrist and contained an impeded potentiometer at its point of rotation Refer to Appendix Figure 2). The potentiometer from both apparatuses recorded voltage from the handle when deviated from neutral. The voltage was fed into and recorded in NeuroScan4.5™. In study A individuals were instructed to hold the handle throughout their wrist extensions while study B required the participant hands to be strapped including all digits to the handle and instructed to allow their hand to rest until they conducted their wrist extensions. In both instances the participants held the handle in a neutral position before contracting, and returned it to this neutral position following contraction.

Exercise

Before performing any exercise the participant was required to fill out the Physical Activity Readiness Questionnaire (PAR-Q; attached) to determine their health status. The participant performed a single 20-minute bout of exercise at 70% of age-predicted maximum heart rate (i.e. maximum heart rate = 220 – age) on a recumbent cycle ergometer. This exercise bout was similar in intensity and duration to the daily aerobic exercise recommended for healthy adults by the Canadian Society for Exercise Physiology in their Canadian Physical Activity Guidelines (McCloskey, Adamo, & Anderson, 2001). Throughout the exercise session the participant attempts to maintain their target heart rate by either self-adjusting their cadence at a constant load (Study A) or through maintaining a constant 60 revolutions per minute (RPM) with changing work load set by the researcher (Study B) . Prior to the exercise session, a short warm-up period of approximately 2 minutes allowed the participant to be

comfortable with the cycle ergometer and allow for them to gradually build up to the targeted workload.

Transcutaneous Electrical Nerve Stimulation

The median nerve of the right wrist was selected for stimulation in order to evoke the N30 somatosensory evoked potential. The nerve electrode was placed on the anterior face of the wrist approximately 5 cm laterally from the midline and then readjusted until a visible thumb twitch was detected. Threshold voltages were detected manually by slowly increasing stimulus voltage until a visible motor twitch was elicited within the thumb. Threshold was determined as the lowest voltage that produced a muscle twitch. Testing stimuli consisted of 1.2x the determined threshold stimulus. The stimulus characteristics consisted of a 0.5 ms square wave electrical pulse, with a 0.75s inter stimulus interval. Stimulation pulses were generated using stimulator (Grass SD-9) controlled by a custom National Instruments LabVIEW™ program that automatically generated the aforementioned pulse characteristics. During stimulation participants were required to keep their hand strapped within the apparatus, resting at the neutral position. Each median nerve stimulation block lasted 300 seconds and consisted of 120 stimulations; providing an adequate amount of data for artifact-free single trial averaging. In total 5 median nerve blocks were conducted, each following a Bereitschaftspotential measuring block. N30 ERP data was produced by epoching continuous the EEG profile between -100 ms prior to and 500 ms post stimulation.

Biometric & Survey Data

Numerous biometric measures were collected including age, sex, weight, height, resting and exercising heart rates in an aim to assess participant's fitness levels. In order to gain accurate fitness assessment the above measures were used in combination to produce a general fitness scores. Height and weight were utilized to generate body mass index scores, while heart rate recovery, total recovery

time and maximum work rate were used to assess cardiovascular capacity. Heart rate recovery was assessed by the difference between the final exercising heart rate and the heart rate decay at 2 minutes following exercise cessation. Total recovery time was determined as the total time required for heart rate to return to baseline levels following exercise cessation.

To provide additional information that was useful to the assessment of fitness, participants were required to complete the self-report International Physical Activities Questionnaire (IPAQ). The long version of the IPAQ contains questions separated into categories such as work, transport, domestic and leisure that assess an individual's duration of sub categorical values in walking, moderate and vigorous levels of physical activity. The IPAQ provides a total physical activity score reported in MET-min/week, and separates these values into three physical activity categories; low, moderate and high. Overall the combined biometric measures and survey data provided a general depiction of individual physical fitness.

Protocol

Subjects were then instructed to perform a ballistic wrist extension, under their own pace every 3-6 seconds continuously for roughly 8 minutes. Following their brisk movement, subjects were told to return to a neutral hand position between reps. In Study B subjects were required to conduct an additional 5 minute block of 120 stimulations from transcutaneous nerve stimulation over the median nerve following each movement protocol. Online EEG recording were amplified and digitized at a sample rate of 500 Hz (Study A) or 1000 Hz (Study B).

After completing resting protocols subjects performed an acute bout of aerobic exercise on a cycle ergometer. Subjects were provided with a 2 minute warm up period, during which the intensity was gradually increased until target heart rate ([220-age]x0.75) was achieved. Once warm up was successfully completed, participants conducted a workout for 20 minutes. During this time period

subjects were instructed to maintain their target heart rate by self-monitoring using a Polaris chest-watch heart monitors and self-adjustment of cadence at a constant workload(Study A) or by researcher adjusted workload while maintaining a constant cadence of 60 RPM (Study B). In both instances heart rate values were evaluated every minute and recorded every 5 minutes. Immediately following exercise cessation, heart rate was measured and subjects were placed back in the booth and instructed to repeat the self-paced movement protocol. Subjects were then provided with a resting period in which their heart rate values and blood pressure (Study B only) were measured continuously until subjects had returned to pre-exercise baseline values. Once a subject had returned to these values, they were instructed to complete the movement protocol either one final time (Study A) or 3 additional repeated movement protocols each separated by 15 minutes of rest (Study B).

4.2.3 Data Acquisition

Electroencephalography (EEG)

A Lycra™ cap containing 64 electrodes placed in accordance with the international 10-20 configuration for EEG electrode placement was utilized for this study. The skin above and below the left eye, and behind the ears were cleaned with exfoliating gel and rubbing alcohol to place electrodes for electrooculography (EOG) and mastoid ground reference. Of the possible 64 channels present on the cap only those of interest (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, and CP4) were prepared and utilized. The electrode cap was actively referenced for collection and then re-referenced to individual mastoid electrodes during analysis. All electrodes (EOG, EEG and mastoids) were filled with conductive gel and all channels had impedances of 5 kΩ or less. EEG was amplified 20,000x and digitized at sampling rate of 500 Hz (Study A) or 1000Hz (Study B) (Synamps2, NeuroScan 4.5, Compumedics) before exporting for post-analysis.

Electromyography (EMG)

EMG was recorded from the right extensor carpi radialis (ECR) muscle using bipolar electrodes placed in close proximity and oriented longitudinally over the muscular belly. Before application of the electrodes the skin was first abraded using an exfoliating gel and rubbing alcohol. EMG was continuously collected at an amplification of 20,000x and digitized at sampling rates coinciding to the sample rates of EEG data in study A or B.

4.2.4 Data Analysis

Movement Related Cortical Potentials

Bereitschaftspotential's were epoched to the onset of muscular contraction as determined visually by a definitive increase in slope followed by muscular burst in EMG recordings. Epoched intervals included -2000 ms prior and 500 ms post muscle onset, while visual inspection allowed the removal of epochs contaminated with blink artifact. Only channels of interest were investigated including Cz and FCz electrode sites. Individual epoch data was then averaged for each subject and group averaged within each condition. Individual Bereitschaftspotential averages were broken down into 4 separated components; Early BP, Late BP, Peak BP and Reafferent potentials and analysis was conducted using either a custom LabView or NeuroScan Program. Early BP onset required a low pass filter of 5Hz conducted on individual BP averages. The first 200ms of the epoch was averaged and provided a comparative baseline against the setting of a 2 standard deviation criterion; the first point of criteria violation in the negative domain was termed onset. In order to evaluate Late BP slope, data was band pass filtered between 0.1-30Hz. Late BP slope was determined by evaluating a 500 ms time window prior to movement onset. Using the same filtered data, Peak BP was established by evaluating the peak to peak difference between the absolute negative peak (time window: -50 to 150ms) and the amplitude at 150 ms prior. Finally RAP amplitude was determined to be the peak to peak difference

between the absolute negative peak (time window: -50 to 150ms) and the greatest positive amplitude in the 400ms following the absolute negative peak. All data was statistically analyzed using one way repeated measures ANOVA.

Short Latency Somatosensory Evoked Potentials

Frontal N30 data was epoched to stimulus onset as determined by an event code from the custom stimulation Labview program during online acquisition. Epoch intervals consisted of -100 pre-stimulus baseline followed by 500 ms post stimulus onset and were extracted from Cz and FCz electrode sites. Individual epochs were visually inspected and those containing blink artifacts were removed. Data was then averaged and a low pass 5 Hz filter was applied. N30 peak data analysis was then conducted using two different methods. Peak N30 was defined as the most negative amplitude during a given time window (25 to 35 ms) in relation to a prestim baseline. N30 amplitude was determined as the Peak to Peak difference between the peak N30 (25 to 35 ms) and peak P20 (18 to 22ms). All data was statistically analyzed using one way repeated measures ANOVA.

Biometric Data

The International Physical Activities Questionnaire data was analyzed in accordance with guidelines for data processing and analysis of the IPAQ. Fitness scores were generated by evaluating participant responses in both duration and intensity of daily physical activities over a typical 7 day week period. Body Mass Index was calculated by dividing the mass (kg) of the individual by the square of the height (cm) and classified using the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults document developed by the National Institute of Health. Exercise biometrics including total recovery time, heart rate recovery, resting heart rate and maximum work rate were also collected and analyzed. Total recovery time was classified as the total elapsed time from the

cessation of exercise to the complete return of heart rate to within 3± beats of rest. Furthermore, heart rate recovery was determined as the total heart rate decay that occurs within the first 2 minutes following the cessation of exercise; calculated by the difference between the final and the heart rate taken 2 minutes after the completion of exercise. As a whole these measures were collective assessed to determine a general measure of total fitness level for each participant.

Electromyography

Raw EMG data was epoched from visually detected onset to 100ms prior and 500 ms post onset. Raw EMG was for each epoch was then placed in a custom LabVIEW™ program for analysis. Data was converted from microvolts to millivolts and band-pass filtered between 20 and 500Hz. EMG signals were then baseline corrected and full-wave rectified. Low-pass filter (6Hz) was then applied and data was smoothed for final analysis. Absolute EMG peak amplitude, area under the curve for the first 200 ms was extracted from the processed data for each epoch and then averaged for each participant for each time condition. In addition time between each movement, termed the inter movement interval was extracted from the continuous data set for each participant, for each time condition, and then averaged. All average data was statistically analyzed using one way repeated measure ANOVA.

Statistical Analysis

In order to appropriately test they original hypothesis that aerobic exercise would induce cortical adaptations within regions responsible for the production of simple movement, identical one way repeated measures ANOVA were conducted on all N30 and BP components (early, late, motor potential and reafferent potential) using IBM SPSS™. Time relative to acute bout of aerobic exercise was selected as the within subject factor and consisted of either 3 (Study A – Pre, Post, and Post(Rest)) or 5 levels (Study B – Pre, Post, Post(Rest1), Post(Rest2) and Post(Rest3)). The dependent measures for each individual analysis included one of either early BP onset, late BP slope, absolute peak BP amplitude,

motor potential amplitude and reafferent potential amplitude. Pre-planned simple contrasts were conducted between all post measures compared to pre values and were reported when main effects existed.

4.3 Results

Study A

Bereitschaftspotential

All subjects (n=11) in all conditions presented with a similar Bereitschaftspotential morphology prior to movement onset. Following offline analysis, approximately 100 epochs per subject per condition were included in the analysis. The greatest absolute BP peak was maximal over the vertex for all conditions (greatest at Cz: Pre; -8.59 μV ± 11.2, Post; -9.31 μV ± 7.1, Post(Rest); -13.38 μV ± 15.3)(Refer to 4a).

Figure 7a depicts the average motor potential amplitude and latency of the peak BP in the Cz electrode of 11 subjects in each independent time measure. The repeated measures ANOVA revealed no main effect of exercise over time on either amplitude ($F_{2,10}$ =0.253, p = 0.779) or latency ($F_{2,10}$ =1.723, p =0.201). The peak BP trended to be more lateralized following exercise with greater values in C3 (-4.34, -6.42, and -8.90) then C4 (-5.86, -5.75,-7.57).

The BP earlier component achieved significant effect of time following exercise in the Cz electrode between time conditions ($F_{2,10}$ = 8.658, p=0.002)(Figure 3b). However, post hoc analysis revealed significant differences only between Pre and Post(Rest) early BP onset ($F_{1,10}$=17.062, p=0.002) and not between Pre and Post conditions ($F_{1,10}$=2.972, p=0.115). The apparent differences in Pre and Post(Rest) conditions are present as an earlier onset of the Early BP component (greatest at Cz: Pre; -1447.89 ms ± 283.3, Post; -1562.54 ms ± 239.3, Post(Rest); -1695.49 ms ± 135.6) depicted in Figure 3b. Further analysis on late BP slope revealed no significant main effect of time on late BP slope ($F_{2,10}$ = 0.414, p=0.666) as shown in Figure 5a. Peak-to-peak analysis between the peak BP and reafferent

potential no significant effects of time on amplitude ($F_{2,10}$ = 2.067, p =0.178) (Refer to Figure 9a). Therefore the current data is suggestive of a selective bias of aerobic exercise on early but not late Bereitschaftspotential morphology and that this effect is delay until heart rate has returned to pre-exercising values.

Biometric Data

Table 1 provides a summary of participant background information along with heart rate measures during exercise. All young healthy subjects (mean age: 27.1 ± 4.76 yoa, mean resting HR: 65.1 ± 7.85 bpm) subjects were able to attain and maintain within a 10% confidence band of their target heart rate. All subjects heart rates returned to within 5 beats of resting values within total elapsed time of approximately 45 minutes following the cessation of exercise (mean time to rest: 46.8 ± 9.72).

Electromyography

Analysis of variance of the EMG data revealed no significant differences across time conditions for the ECR absolute peak amplitude ($F_{2,10}$ = 2.462, p=0.113; Pre= 0.762 mV ± 0.13, Post= 0.0998mV ± 0.02, Post(Rest)= 0.0751mV ± 0.01). This data suggests that the ECR activity was static and is comparable across Pre, Post and Post(Rest) time conditions. Furthermore, inter-movement intervals were not significantly altered across differing time conditions ($F_{2,10}$ = 0.267, p=0.770; Pre= 4.40 sec ± 0.38, Post= 4.14 sec ± 0.027, Post(Rest)= 4.36 sec ± 0.33), indicative that participants were able to maintain similar pace during each testing block. Finally an analysis of the ballistic nature of movement revealed non-significant differences between time conditions for the area under the curve of the first 200 ms of EMG activity ($F_{2,10}$ =0.362, p=0.701; Pre= 15.56 ± 2.41, Post= 16.89 ± 2.95, Post(Rest)= 15.44 ± 4.88). Overall this data suggests that participants did not alter their movement characteristics during trials.

Study B

Bereitschaftspotential

All subjects included in analysis (n=10) presented with similar Bereitschaftspotential morphology occurring prior to EMG onset, except 2 individuals who presented with no early BP while all other BP characteristics including late and reafferent BP components remained intact. For the purpose of analysis these 2 subjects were removed from Early BP onset evaluation but remain in late BP analysis. Following post-analysis blink removal, an average of 120 epochs per subject per time condition contributed to individual averages. Peak BP was maximal over fronto-central electrode sites (Cz: Pre; -11.86 μV ± 3.3, Post; -9.81 μV ± 2.0, Post(Rest1); -11.41 μV ± 3.0, Post(Rest2); -11.69 μV ± 2.9, Post(Rest3); -12.52 μV ± 2.37). All Bereitschaftspotential's were categorized into 4 sub components including Early BP, Late BP slope, Peak BP and Reafferent Potentials.

A one way repeated measures ANOVA revealed a main effect of time following aerobic exercise on Early BP (N=8; $F_{4,7}$=3.370, p=0.023), masked as alterations in earlier onsets. Pre-planned contrasts confirmed results from study A with similar changes to Early BP onset and Late BP over time at the Cz electrode site. When compared to Pre-BP measures, non-significant changes existed immediately after exercise cessation in the Post time condition ($F_{1,7}$=2.899, p=0.132). However significant differences were observed when heart rate returned to baseline at Post(Rest1) ($F_{1,7}$ =46.597, p=0.00001), and was sustained for up to 30 minutes, in Post(Rest2) ($F_{1,7}$ =10.060, p=0.016) and Post(Rest3) ($F_{1,7}$ =9.099, p=0.019). When Early BP data between study A and B were normalized and collapsed across time conditions Pre, Post and Post(Rest1) a main effect of exercise over time is revealed immediately after exercise (Post time condition) ($F_{1,18}$ =4.950, p=0.038) and at the Post(Rest1) condition ($F_{1,18}$ =38.119, p=0.0001). This provides additional support that exercise produces a graded response during the recovery and not onset at Post(Rest1) as depicted in study A. Further analysis affirmed Study A results with no observed main effect of time on Late BP slope ($F_{4,9}$=1.277, p=0.290), peak to peak BP amplitude

($F_{4,9}$=0.287, p=0.884) or latency ($F_{4,9}$=1.053, p=0.351) at the Cz electrode site. Finally reafferent potential data processing at the Cz electrode site revealed a significant main effect of time on peak to peak amplitude ($F_{4,9}$=2.722, p=0.045) but not on latency ($F_{4,9}$=0.673, p=0.615). Pre-planned contrasts discovered significant difference in Post ($F_{1,9}$=15.402, p= 0.003), Post(Rest1) ($F_{1,9}$=6.778, p=0.029), Post(Rest2) ($F_{1,9}$=8.349, p=0.018) and Post(Rest3) ($F_{1,9}$=5.351, p=0.046) when compared to Pre amplitude values. Upon further investigation the main effect of time on motor evoked sensory information is depicted by a decrease in overall RAP amplitude sustained over all post exercise time measures (Cz: Pre; -16.16 μV ± 3.5, Post; -12.96 μV ± 4.6, Post(Rest1); -12.90 μV ± 4.2, Post(Rest2); -12.91 μV ± 6.1, Post(Rest3); -12.63 μV ± 4.68). The current data provides further support that an influence of acute bout of aerobic exercise does exist on early motor preparation but not motor execution and suggests a possible effect of exercise on motor evoked sensory processing areas.

Short Latency Somatosensory Evoked Potentials

All participants (n=12) had a positive P20 and negative N30 peaking over fronto-central (FCz, and Cz) electrode sites. A one way repeated measure ANOVA revealed no main effect of time in absolute peak N30 amplitude at Cz ($F_{4,11}$=1.498, p=0.246) or FCz ($F_{4,11}$=1.211, p=0.321) electrode sites. Further peak to peak analysis between N30 and P20 presented no main effect of time on N30 amplitude at FCz ($F_{4,11}$=1.322, p=0.278) or Cz ($F_{4,11}$=2.07, p=0.103) following aerobic exercise.

Biometric Data

Table 2 provides biometric data used to assess general levels of fitness for all participants. Data values include Body Mass Index, International Physical Activities Questionnaire response (IPAQ), Heart Rate Recovery, Resting Heart Rate and Maximum Work Rates. IPAQ data presents weekly physical activity in MET·min·week^{-1}. Subjects self-reported total physical activity was classified as moderate to

high activity (Mean: 4538.18 MET·min·week^{-1}; SEM: ± 660.11) which was an accumulation of the individuals weekly walking, moderate and vigorous physical activity. Most of the physical activity self-reported was classified as vigorous (Mean: 2174.55 MET·min·week^{-1}; SEM: ± 584.48) followed by moderate (Mean: 1388.20 MET·min·week^{-1}; SEM: ± 441.47) and walking (Mean: 975.00 MET·min·week^{-1}; SEM ± 233.07). Participants on average were within a normal ranged Body Mass Index (Mean: 24.61 kg/m^2; SEM: ± 0.95), with only two participants being classified as overweight and one as obese. Resting heart rates on average were 63.45 bpm (SEM: ± 1.76), a value that is within the normal healthy range for this age group (Kannel et al, 1987). Maximum work rates achieved during exercise ranged from level 1 to 13 on the recumbent bike with a mean of 5.09 levels (SD: 3.59 levels) maximally achieved. Participant recovery times averaged roughly 45 minutes (Mean: 42.45 min; SD: ± 10.75), which coincides with results from study A. Heart rate recovery was assessed as a general measure of cardiovascular competency with a mean beat difference of 46 bpm (SD: ± 10.75 bpm) from exercising to 2 minutes post exercise. All in all participant biometric data suggests a general categorization of healthy to high fit individuals. Finally due to the confounding concerns of sweat on EEG electrode impedance conductance and electrode resistance was measured before conducting every testing block. Non-significant differences were determined after exercise in resistance of electrode site of in 8 subjects involved in study 2 ($F_{4,7}$ = 1.361, p=0.273; Pre= 0.44 KΩ sec ± 0.610, Post= 1.15 KΩ ± 0.179, Post(Rest)= 0.3875 KΩ ± 0.185, Post(Rest2)=0.51 KΩ ± 0.28, Post(Rest3)=0.51 KΩ ± 0.185).

Electromyography

Analysis of the EMG data revealed that no significant differences existed between conditions for the ECR absolute peak amplitude ($F_{4,7}$ = 2.978, p=0.112; Pre= 0.303 mV ± 0.03, Post= 0.236 mV ± 0.03, Post(Rest1)= 0.231 mV ± 0.02, Post(Rest2)=0.243 ± 0.03, Post(Rest3)=0.235 ± 0.03). This data suggests, like study A, that ECR activity was similar across different time conditions when compared.

Furthermore, inter-movement intervals were not significantly altered across differing time conditions ($F_{4,7}$ = 1.992, p=0.123; Pre= 4.15 sec ± 0.35, Post= 3.85 sec ± 0.36, Post(Rest)= 4.31 sec ± 0.29, Post(Rest2)=4.10 sec ± 0.28, Post(Rest3)=3.93 sec ± 0.28), indicative that participants were able to maintain similar pace during each testing trial. Finally an analysis of the ballistic nature of movement revealed non-significant differences between time conditions for the area under the curve of the first 200 ms of EMG activity ($F_{4,7}$ =3.548, p=0.091; Pre= 35.89 ± 3.02, Post= 26.25 ± 2.71, Post(Rest)= 25.39 ± 3.00, Post(Rest2)=26.01 ± 4.43, Post(Rest3)= 26.0794 ± 5.12). Overall as with study A this data suggests that participants did not alter their movement characteristics across time.

4.4 Discussion

Previous findings combining acute aerobic exercise and event related potentials have shown convincing evidence in support for enhancements in cortical processing (Brisswalter et al, 2002; Kamijo et al, 2009). The current study utilized the Bereitschaftspotential to determine whether or not cortical excitability was modulated following an acute bout of aerobic exercise and to establish a time line in relation to other physiological markers such as heart rate. The main findings of this study partially support the original hypothesis that aerobic exercise was capable of altering cortical excitability within regions that are involved in self-paced movement production. However, the exercise-induced effect on early BP morphology revealed an adaptation that differed from previous ERP literature, moreover this effect was sustained for significant periods of time.

In this study, subjects performed a 20 minute bout of aerobic exercise at a moderate intensity (70% age predicted maximum heart rate) on a recumbent cycle ergometer; a similar intensity and duration to the daily recommended exercise for healthy adults by the Canadian Society for Exercise Physiology (Warburton et al., 2007). This exercise protocol was sufficient in raising the participant's heart rate to roughly 70% of their age predicted maximum heart rate for a sustainable period of time,

with no participants reporting any level of fatigue. Previous work using acute aerobic exercise and event related potentials have shown an intensity dependent relationship, where ERP's appear most sensitive to changes occurring after moderate intense bouts (Brisswalter et al, 2002; Kamijo et al, 2004a; McMorris & Hale, 2012). Furthermore the exercising protocol differed between study A and B, where study A required the participant to monitor and respond to changes in their own heart rate, study B provided no biofeedback in order to achieve and maintain a target heart rate. Following a mixed one-way ANOVA, no significant differences were determined due to changes to the exercising protocol between the two studies. This allowed for the data to be collapsed across studies and revealed with regards to the early BP, that significant differences were determined at the immediate post measure which did not appear in the original analysis. Finally, the exercise protocol required the use of the lower limbs, the rationale for this selection was two-fold. First in an effort to remove confounding or fatiguing factors associated between the aerobic exercise limb and the limb recruited for the elicitation of the BP as previous research has shown that fatigue can alter BP morphology (Dirnberger et al, 2004). Second to provide similar exercising comparisons to those previously mention in cognitive research that requires the use of the legs for purposes of driving an aerobic exercise effect (Yagi et al, 1999; Magnié et al., 2000; Kamijo et al, 2004a; Kamijo et al, 2009; Davranche et al, 2009; Roig et al, 2012).

Results from study A suggest that early and not late component BP is influenced by a moderately intense acute bout of aerobic exercise; a result that was reinforced by study B. Repeated measures ANOVA revealed a main effect of time following aerobic exercise on the onset of the early component BP in both studies. In addition this effect seems more prominent even after other physiological markers such as heart rate have returned to pre-exercise baseline measures. In other words, the onset of the earlier BP appears to be modulated slightly by aerobic exercise immediately following, and becomes significantly earlier roughly 45 minutes after exercise cessation; this effect is maintained at least 30 minutes following the resting condition depicted by study B. Interestingly, the

effect of the exercise appears to be selective in altering only the early component, with no significant modulations developing in late BP slope, or motor potential. However, due to the limitations of the BP in detecting scalp recordings, it is possible that the BP was not sensitive enough to determine subtle changes in motor execution areas such as M1; further investigation is recommended. Further analysis revealed contradictory results with regards to the reafferent potential amplitude between studies A and B. The current data from study B is suggestive of an influence of aerobic exercise on motor related sensory processing, and under further investigation it appears to suppress the amplitude of the reafferent potential. Due to the lack of consistency between studies A and B, the possible difference in this potential could be representative of increased noise during the Pre time condition which made it appear more positive; this is likely since all post mean amplitudes are nearly identical. However the frontal N30 showed similar characteristics of suppression but never reached significance. Although not conclusive this interesting finding provides basis for further investigation into a possible effect of aerobic exercise on tactile stimuli processing.

Furthermore it is well accepted within the literature that BP measures are sensitive to changes in movement profiles (see review, Shibasaki et al, 2006). In the current study subjects were requested to produce a ballistic wrist extension of similar magnitude and direction. All EMG profiles for amplitude, pace and ballistic nature in all subjects reported no significant differences over time through the entirety of the testing blocks. This reassures that changes seen to early BP are not related to alterations in movement characteristics between the separated measurements. Finally, an emerging body of evidence supports that fitness plays a critical role in assessing cognitive markers (P300 & CNV) (Brown et al, 2010; Eskes et al, 2010; Kamijo et al, 2010; Stroth et al, 2009), therefore biometric data was collected to evaluate possible fitness levels. In general participants reported a higher than average physical activity profile which corresponded to normal Body Mass Index scores and heart rate recovery values. Combined these results indicate that individuals within this study can be classified as average to higher

fit. Due to lack of research on aerobic fitness it is difficult to speculate on the possible roles that fitness may have on altering the BP, even in the absence of an acute bout of aerobic exercise. However, as mentioned above fitness does appear to alter other neuroelectric markers, and therefore a possibility exists for adaptations within movement related circuitry.

To our knowledge, the current study is the first to show that a moderately intense bout of aerobic exercise alters early motor cortical processing. The discovery of this influence is in support of previous findings using cognitive ERP's such as the CNV (Petruzzello et al, 1997) and P300 (Hillman et al, 2003). However, the temporal nature of this effect versus those previously seen cannot be compared. Recent findings using the CNV (Kamijo et al, 2004) and P300 (Kamijo et al, 2009; O'Leary et al, 2011) have only identified differences in the minutes immediately following a short bout of aerobic exercise, typically these values return to pre-exercising values following a reduction in heart rate. The current investigation sought to develop a time-course for the exercise-induced effect. In support for the initial hypothesis an acute bout of aerobic exercise was sufficient in eliciting an adaption immediately after aerobic exercise (appearing when data was collapse across studies) however, contrary to the original hypothesis, exercise-induced adaption to early movement related cortical activity remained elevated for up to 30 minutes after heart rate had returned to baseline. This sustained influence of aerobic exercise raises interesting questions about the possible underlying neural mechanisms that drive this particular exercise-induced effect.

Recent meta-analytical models have attempted to provide a foundation for neural mechanisms behind the influence aerobic exercise has on cognitive markers (McMorris et al, 2012). An emerging model known as the Reticular Activating Hypofrontality model, developed by Dietrich and Audiffren (Dietrich & Audiffren, 2011), has gained recent popularity within cognitive literature. This model aims to explain the combination and synergistic role aerobic exercise has on enhancing arousal and decreasing

conflicting cognitive pathways. This is achieved by increased activity within the reticular activating process and suppression of activity within the prefrontal regions. However, one major limitation to this model is the time period for which it was designed to explain; during or immediately following aerobic exercise. Further reports have suggested that aerobic exercise influences the reticular activating process by direct connections between brainstem areas that control heart rate and breathing; historically both heart rate and arousal have been intimately associated with one another. In the current study we aimed to use heart rate as a general measure of increased arousal state following aerobic exercise. Therefore it is possible that arousal may responsible for the initial changes in BP morphology seen immediately after exercise however due to the combination of both the limited time window of the RAH model and the temporal nature of the exercise-induced effect to be maximal on the Bereitschaftspotential to occur after heart rate had returned to rest, it may be inadequate to explain the delayed adaptions seen to BP morphology by any short term arousal effect.

Due to the selectivity of aerobic exercise to modulate early but not late motor related cortical activity a more appropriate model can be suggested based on other research that shows specific influences to early BP morphology. Previous reports in Parkinsonian patients have shown that the early BP is greatly attenuated or non-existent while the later BP component remains unchanged or is larger than normal (Dick et al., 1989). Moreover other event related potentials such as the N30 appear to be influenced by detriments in basal ganglia processing with Parkinsonian patients suffering from a decreased or absent N30 (Boecker et al, 1999). Generally speaking the Early BP represents generation output from SMA while the N30 represents input of which both activities appear intimately coupled to basal ganglia function.

Recent support has shown that both in combination with regular PD medication (Bergen et al, 2002) and when medication is removed (Muller, 2010), continuous bouts of acute aerobic exercise not

only improves cardiovascular function but also alleviates common symptoms of akinesia and bradykinesia when compared to age and behavior matched controls. The authors proposed that this improvement in movement initiation was related to the influence aerobic exercise may have on altering dopamine synthesis within the basal ganglia and eventually the corticostriatal motor pathways utilized in motor preparation. This stems from the finding that both early and late BP components are differentially sensitive to pharmacological manipulation, where acute administration of dopaminergic medication increases the amplitude of early but not the late BP in healthy controls (Dick et al, 1987). Further research involving healthy rat specimens lends additional support for this hypothesis; showing increases in dopamine and neurotransmitter synthesis within basal ganglia networks during an acute bout of exercise (Kindermann et al, 1982; Chaouloff et al, 1989; Meeusen et al, 1995). Moreover, this exercise-induced neurotransmitter synthesis is a graded response becoming maximal during the recovery period for dopamine and other neurotransmitters such as cortical serotonin 40-60 minutes post exercise (Hattori et al, 1994). This is reinforced with from the current results that shown when in combination study A and B show a graded response of exercise throughout recovery. Efforts to translate this dopaminergic effect into human models have yet to be successful (Wang et al, 2000). However, as with arousal, neurotransmitter and hormone release appear to be subject to changes in intensity with most optimal neurotransmitter release-effects occurring at moderate intensities. Based on this understanding, the experimental and exercise parameters by Wang (Wang et al, 2000) may not have been sensitive enough to detect or promote dopamine fluctuations: (1) because the exercise fell well into the high intensity range (85% age predicted maximum heart rate) and (2) PET is not sensitive enough to detect that low level changes typically associated with dopamine concentration. In comparison to Wang and colleagues (2000) the current study used a moderate bout of aerobic exercise (70% age predicted maximum heart rate) and saw measurable enhancements to SMA an effect that was delayed until approximately 45 minutes following aerobic exercise cessation. Due to the nature of the

SMA to be intimately coupled to basal ganglia output it is plausible based on current rat models that aerobic exercise induced a dopamine effect that alters basal ganglia output and manifests as early changes in SMA activity.

As mentioned previously, parkinsonian patients who conduct moderate aerobic exercise see measurable alleviations of symptomology following the recovery time of exercise (Bergen et al, 2002; Muller et al, 2010). It has long been proposed that akinesia results from an increased tonic inhibition of thalamocortical neurons that renders the projected area less responsive to other inputs involved in the generation of movement initiation (Bermanzohn et al, 1992). Furthermore when movement production does occur, it suffers greatly by an increase in system noise produced by the inadequacy of the motor system to filter out inappropriate signals; producing unresolved movements. Therefore in the case of the present study, it can be hypothesized that aerobic exercise may enhance the signal to noise ratio of SMA activity manifesting as an earlier onset. Furthermore, the delayed exercise-induced effect could be related to increases in dopamine release, which have also been shown to be delayed following short bouts of aerobic exercise in animals (Hattori et al, 1994). Interestingly enough, aerobic exercise maintenance of a selective influence goes beyond just separation between different nodes but exist between different information within the same networks. In the present case SMA motor output was selectively enhanced by aerobic exercise while motor related sensory information remained relatively unchanged; depicted as no change in the N30. This proposes that within the parkinsonian model, an acute bout of aerobic exercise would retain the ability to recapture the early BP potential during periods of healthy movement initiation but have no effect on recapture of the N30; to date no known study exist.

Nevertheless the dopaminergic mechanism represents just one of many possible mechanisms to explain current results and due to a current absence of literature within the field of aerobic exercise and

MRCP's we can only speculate on plausible underlying mechanisms. The difficulty in interpreting the current data is further complicated by the fact that the influence appears to be delayed. Of the little research that identifies aerobic exercise and motor cortical processes, no known research describes a delayed influence with regards to other neuroelectric markers. Almost all research concerning a delay in effect due to acute aerobic exercise demonstrates the regulation of biochemical signals. In addition to the possible dopaminergic mechanism described previously, another molecule known as BDNF appears to be susceptible by aerobic exercise. Both human (Ferris et al., 2007) and animal studies (Gomez-Pinilla, 2002) have described an intimate relationship between BDNF concentration and acute aerobic exercise. Overall BDNF's influence appears to be driven by an enhancement in excitatory glutamatergic cells and a suppression or down regulation of inhibitory GABAergic cells (Binder et al, 2004). For this reason BDNF provides an attractive mechanism for adaptions to cortical excitability; shown within this thesis. However further investigation is required in order to determine possible underlying BDNF mechanisms within motor regions as current work in this area has been limited to neurons of the hippocampus. In addition most research characterizing the role of BDNF on neuron processing and transmission is related to its unique ability to interact during the process of synaptic plasticity; a process requiring repetitive training sessions. Although it is plausible that aerobic exercise induced a BDNF response altered motor cortical excitability within motor preparatory areas it is unlikely that the results of the current studies are due to any changes in motor learning or synaptic plasticity, since the simplicity of the task used to elicit the BP should not be adequate in eliciting changes in motor learning.

Of the numerous possible mechanisms, we can only speculate as to the likelihood of each of the existing models to current results. The first mechanism relates to that fact that aerobic exercise provides a physiological response that produces changes frontal central cortical arousal levels, some suggest that these changes are due to changes in catecholamines. With relation to the current data this suggests that arousal enhanced the receptive nature of the SMA to incoming motor preparatory

information from other secondary motor centres. This theory adds support for adaptations immediately after exercise but does not adequately provide an understanding of changes following the resting conditions. The second mechanism is similar in nature to the previous arousal hypothesis with respect to its dependency on aerobic exercise inducing a change in neurotransmitter release. The dopaminergic mechanism is based on current parkinsonian and rat models revealing increased changes in dopamine concentration following acute aerobic exercise and changes in dopamine are capable of providing early BP adaptations in the absent alterations to late BP. Furthermore dopamine release after exercise can remain elevated for similar time course to the aerobic exercise effect witnessed in the current study. This theory proposes a bottom up mechanism, by which an induced enhancement to the basal ganglia (GPi and SNr) output loops reduces the tonic inhibition to the supplementary motor area enhancing the signal to noise ratio within the system. Finally, the last discussed mechanism is related to a well-known neurotrophic factor that is sensitive to modulation by aerobic exercise; BDNF. The BDNF theory being that aerobic exercise enhanced BDNF concentration resulting in an induction of cortical excitability within motor preparatory circuits. Further, BDNF as with dopamine have been shown to remain elevated for substantial periods of time during the recovery period following acute bouts of aerobic exercise. The induction of an enhanced synaptic transmission within SMA neurons could be responsible for results shown within this study. However caution is warranted when drawing conclusions based on these mechanisms as the BP is only sensitive to cortical level changes in SMA and M1. In addition, more sensitive markers for both of these two cortical areas do exist such as intracortical recordings and transcranial magnetic stimulation. The current data set only provides a foundation for further research investigation into the underlying neural mechanisms of aerobic exercise on self-paced MRCP's and the identification of this effect using other possible neurological tools. With all results taken together, we conclude that acute bouts of moderately intense aerobic exercise provides a selective and delayed adaptation to early motor related cortical output. The proposed outcome of this effect is an increase in

the efficiency of processing of SMA activity prior to simple movement production driven by a possible bottom up mechanism via enhanced basal ganglia function.

CHAPTER 5: SUGGESTIONS FOR FUTURE STUDIES

In brief the purpose of the current thesis was to provide a base for expansion of the effects of aerobic exercise on current cognitive ERP's into movement related cortical potentials. To the best knowledge, this study is the first known to combine movement related cortical potentials with aerobic exercise. Future studies in healthy subjects are required and should include investigations into how aerobic fitness, aerobic training, and exercise intensity and duration influence MRCP's. In an effort to provide a further support for current findings future studies should also include expansion into movement disorders related to movement generation, such as Parkinson's disease. The current findings suggest that the BP may provide in addition to behavioral measures, a sensitive and quantifiable cortical measure that can be used to establish possible mechanisms underlying current benefits seen by parkinsonian patients following acute aerobic exercise.

Table 1: Summary of Participant Physiological Characteristics Study A (Note: "-" corresponds to missing data.).

Subject	Sex	Age	Resting HR	TRGT HR	Heart Rate at Separate Time Points During Exercise (BPM)						Time to Rest (min)
					1	5	10	15	20	AVG	
1	F	27	69	135	141	138	137	140	137	138.6	-
2	F	22	62	139	119	129	120	125	128	124.2	43
3	M	32	67	132	116	127	132	135	132	128.4	46
4	F	28	55	134	144	147	142	145	134	142.4	50
5	M	24	76	137	134	139	142	135	145	139.0	-
6	M	22	56	139	109	128	128	131	140	127.2	47
7	M	23	71	138	119	138	140	141	138	135.2	36
8	M	38	70	127	127	121	126	131	123	125.6	38
9	M	27	75	135	140	139	134	137	136	137.2	55
10	F	29	60	133	67	133	-	140	138	119.5	67
11	F	26	55	136	74	138	142	139	136	125.8	39
Average		27.1	65.1	135	117.3	134.3	134.3	136.3	135.2	131.5	46.8
Standard Deviation		4.76	7.85	3.52	25.78	7.39	7.71	5.65	5.93	7.16	9.72

Table 2: Summary of Participant Biometric Data from Study B.

Subject	Sex	Age	IPAQ Score	Physical Activity	Rest HR	Post HR	to 1 min	BMI	BMI Score
12	M	23	3506	High	50	75	37.5	24.04	Normal
13	M	20	3335	High	59	96	48	21.29	Normal
14	F	22	6402	High	62	83	41.5	24.24	Normal
15	M	20	4788	High	60	121	60.5	23.77	Normal
16	F	24	8520	High	60	90	45	22.60	Normal
17	F	25	1926.5	Mod	59	104	52	22.47	Normal
18	F	29	5295	High	69	104	52	24.50	Normal
19	M	26	6183	High	71	100	50	27.66	Overweight
20	M	29	6085.5	High	63	103	51.5	30.78	Obesity
21	F	22	1821	Mod	77	110	55	20.69	Normal
22	M	24	2058	Mod	68	120	60	28.71	Overweight
Avg		24	4538.182		63.45455	100.5455	50.27273	24.62	
SEM		3.579191	660.1088		2.213034	4.273308	2.136654	0.95487564	

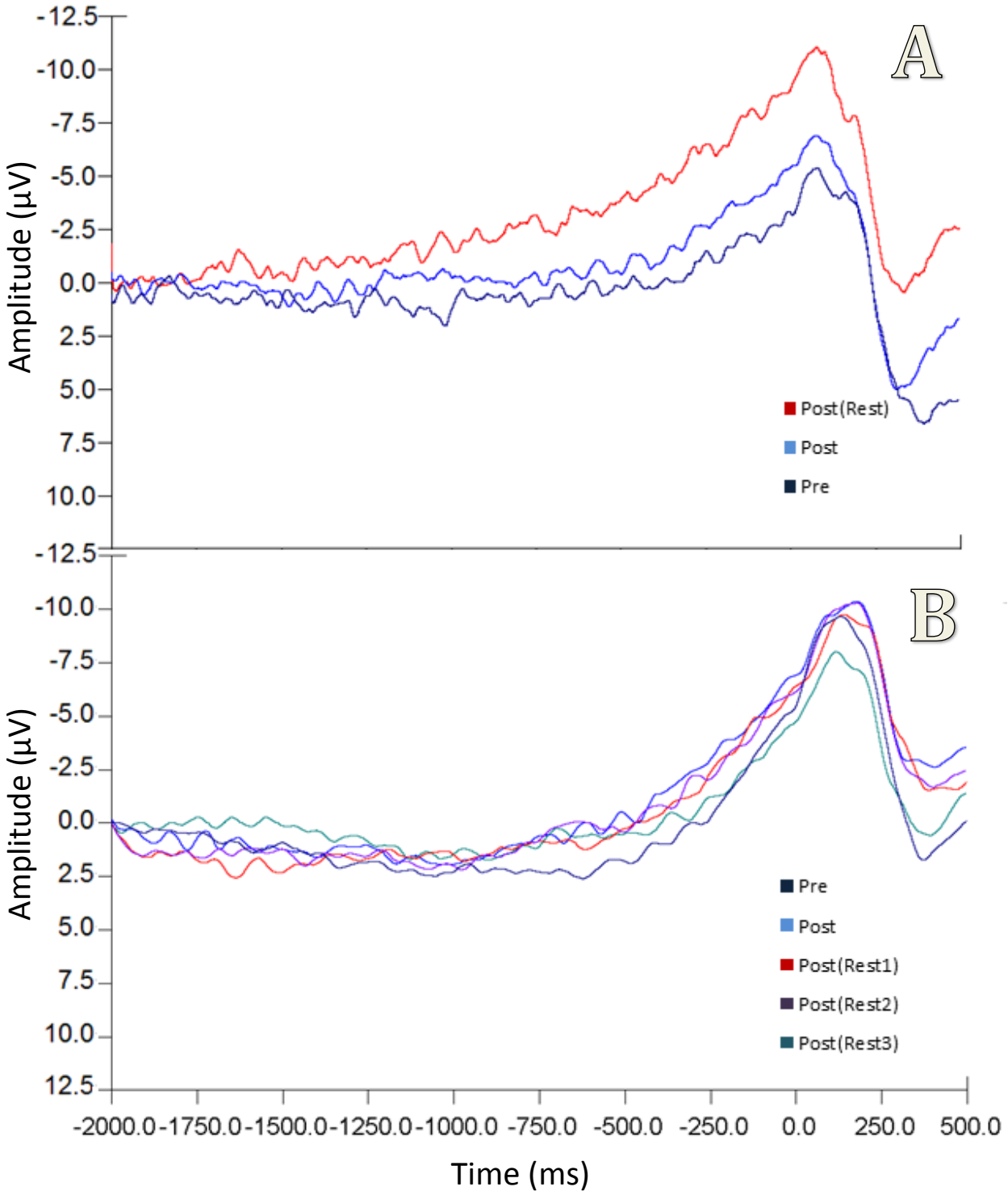


Figure 1: Bereitschaftspotential recordings are shown for 3 (Study A) or 5 (Study B) grand average tracings represent various time points surrounding an acute bout of aerobic exercise; preceding (Dark Blue), immediately following (Light Blue), return to baseline heart rate measures (Red), additional 15 minutes (Purple) and 30 minutes (Turquoise). Tracings are grand averages of 11 (A) and 10 (B) subjects at the Cz electrode site.

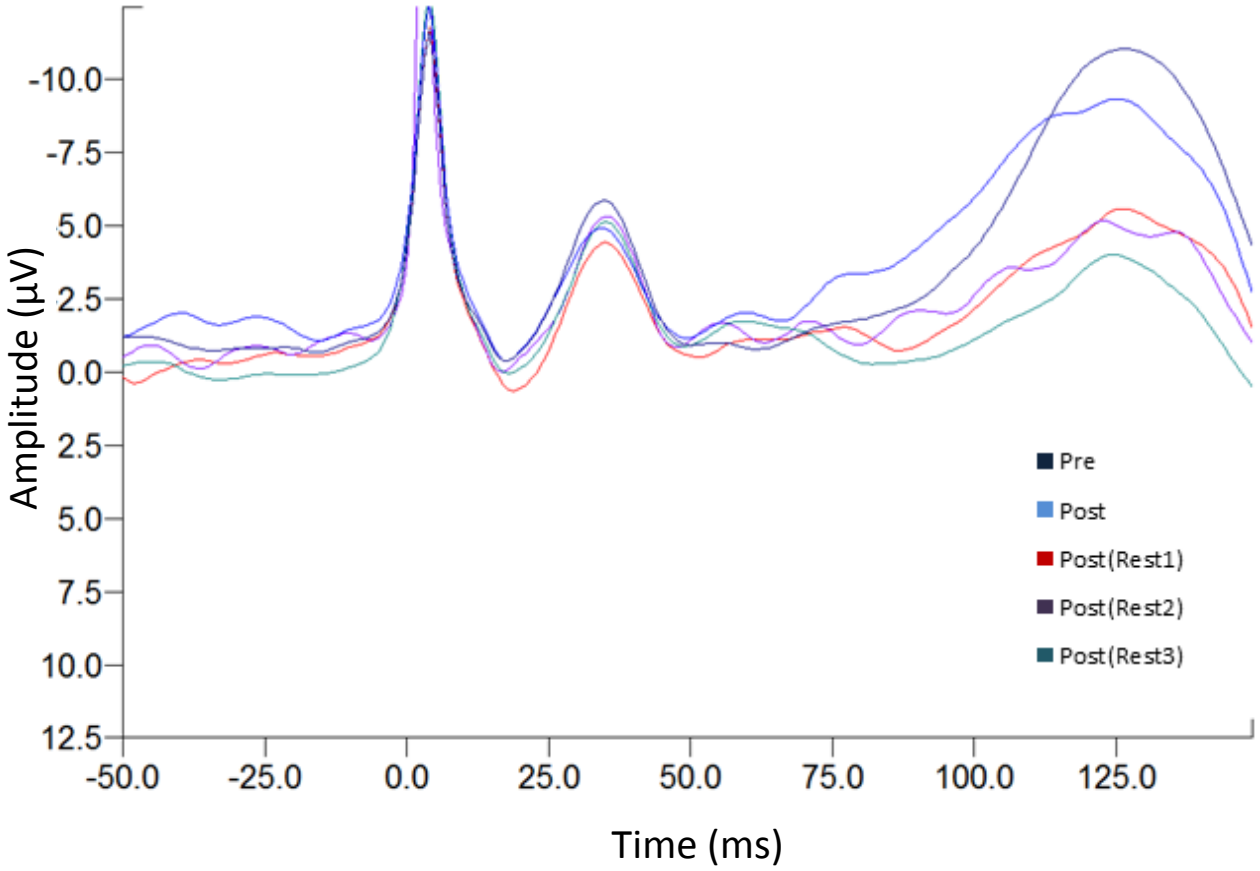


Figure 2: Grand average (N=12) N30 somatosensory evoked potential recordings are shown for 5 overlaying tracings representing various time points surrounding an acute bout of aerobic exercise; pre exercise depicted as dark blue, immediately following exercise cessation in light blue, return to heart rate baseline in red, and an additional 15 minutes following Post(Rest1) measurements in purple and 30 minutes following Post(Rest1) in turquois.

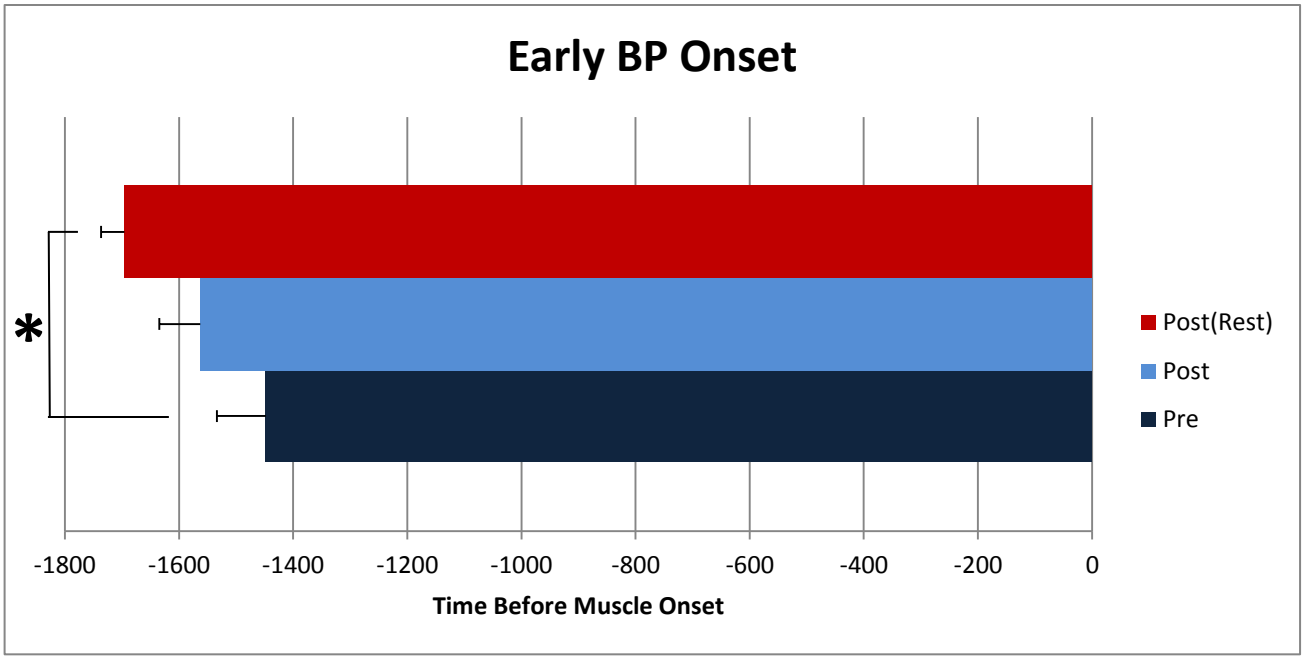


Figure 3a: Average (N=11) Early BP onsets for Cz electrode across time. Onset determined as 2x the standard deviation of a baseline (first 200ms) mean. (* = significant difference, p<0.05)

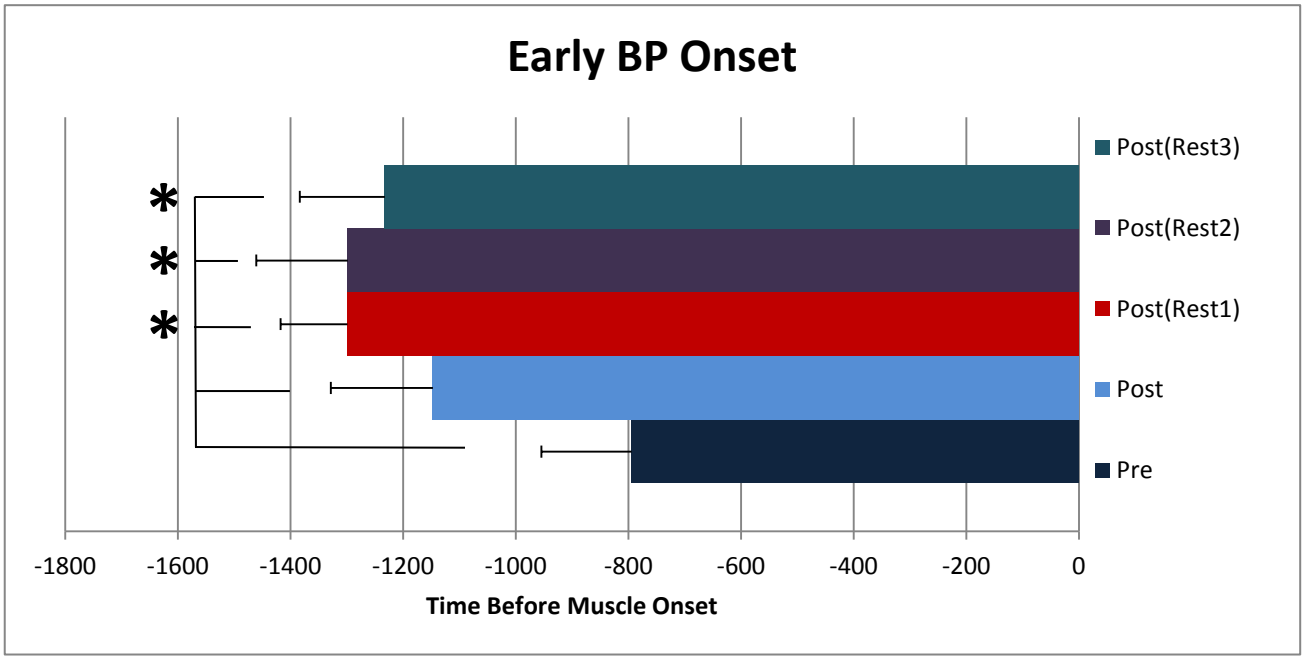


Figure 3b: Average (N=8) Early BP onsets for Cz electrode across time. Onset determined as 2x the standard deviation of a baseline (first 200ms) mean. (* = significant difference, p<0.05)

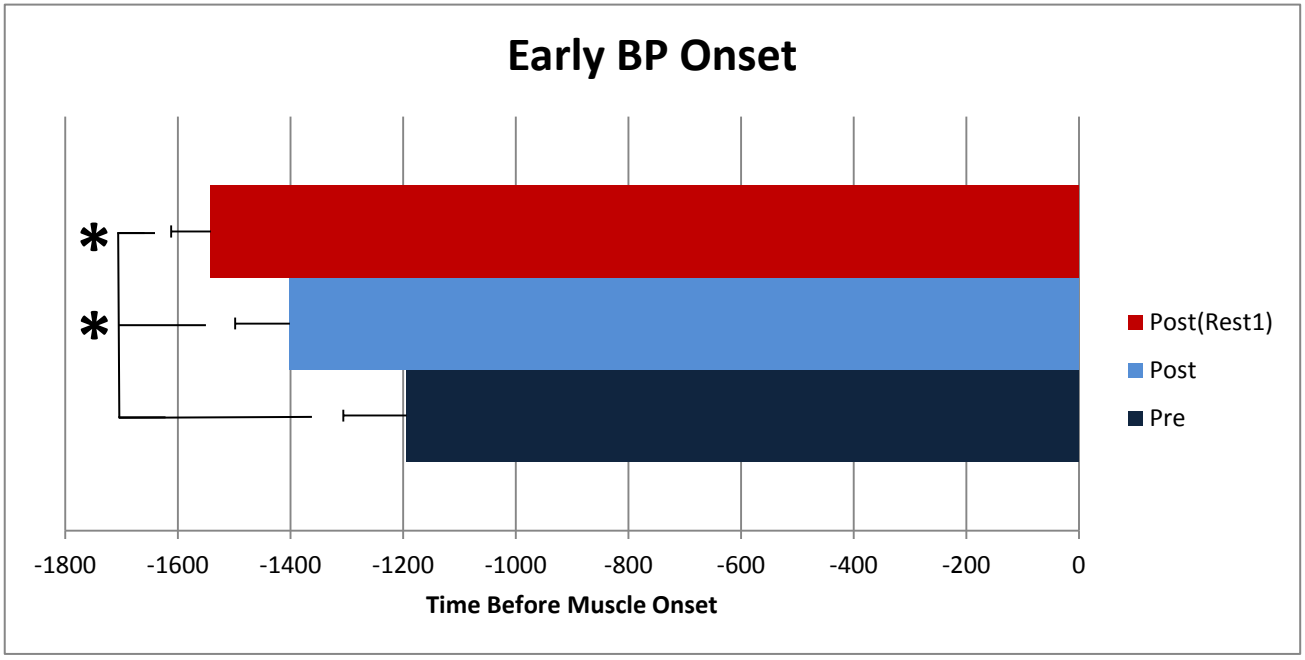


Figure 4: Average (N=19) Early BP onsets for Cz electrode across time for combined data sets between study A and B. Onset determined as 2x the standard deviation of a baseline (first 200ms) mean. (* = significant difference, $p<0.05$)

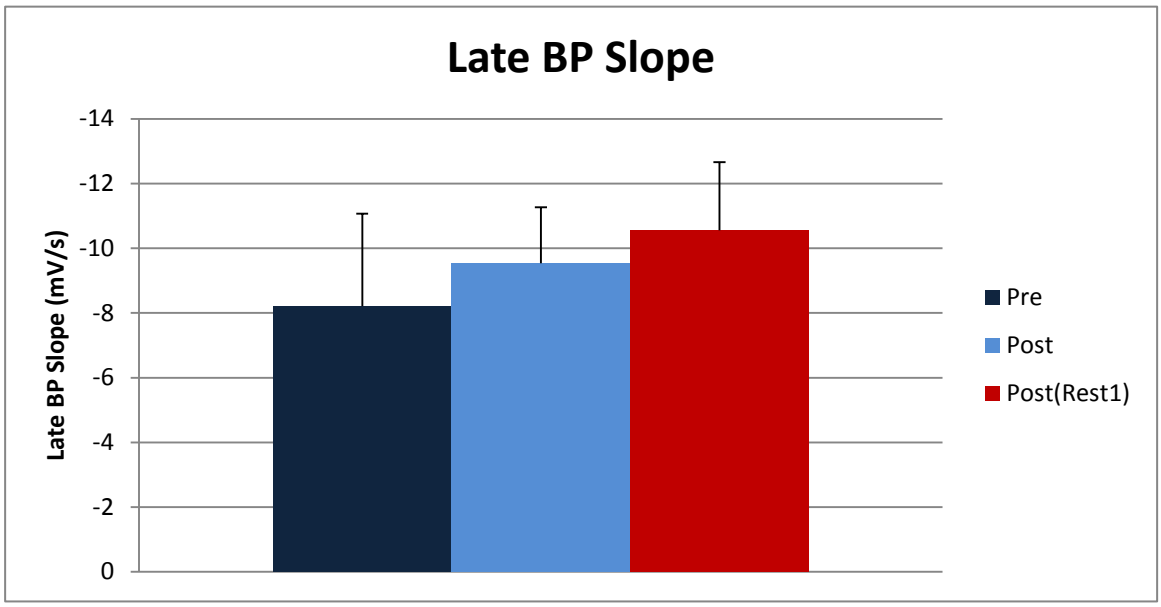


Figure 5a: Average (N=11) BP slope at Cz electrode site across time. Slope was determined over the 500ms prior to EMG onset.

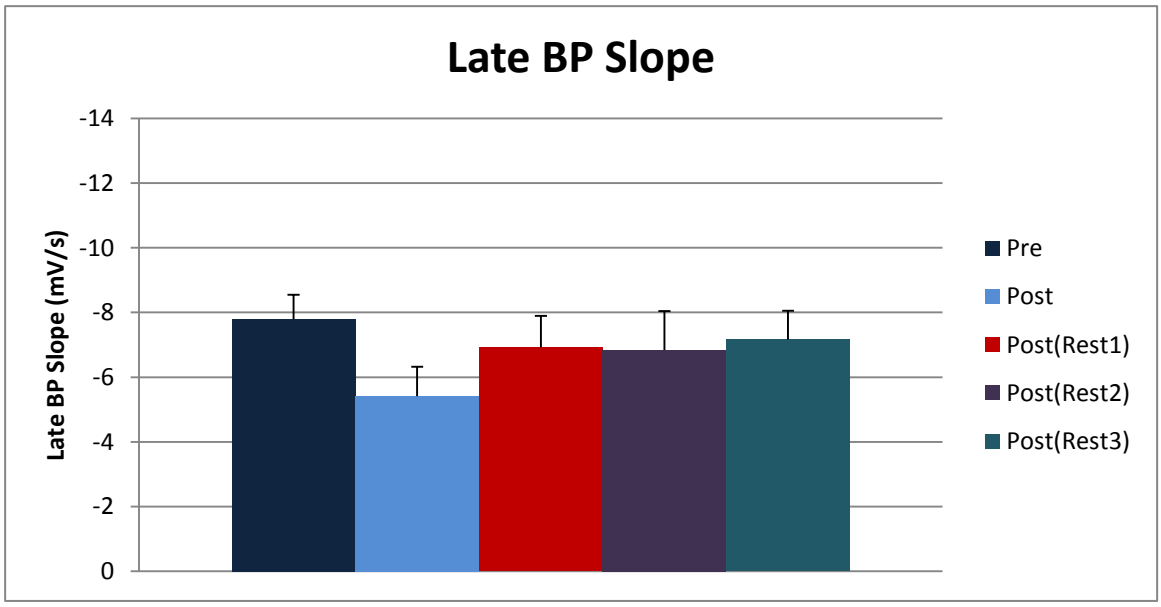


Figure 5b: Average (N=10) BP slope at Cz electrode site across time. Slope was determined over the 500ms prior to EMG onset.

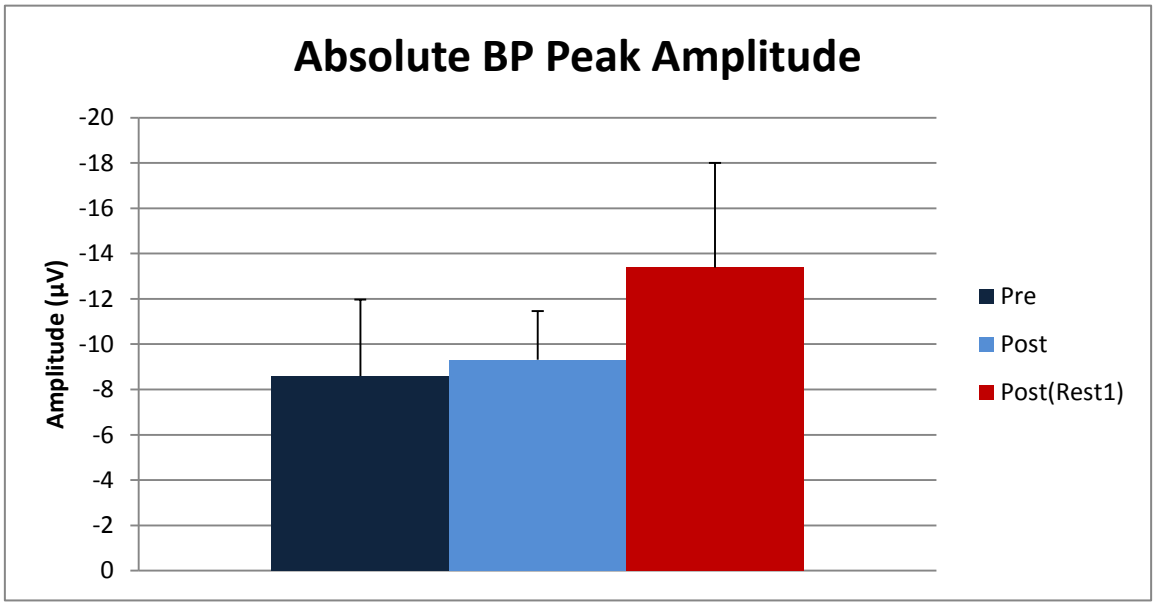


Figure 6a: Average (N=11) absolute peak BP at Cz electrode site across time. Absolute peak BP determined as peak negative deflection between -100 and 200 ms surrounding EMG onset.

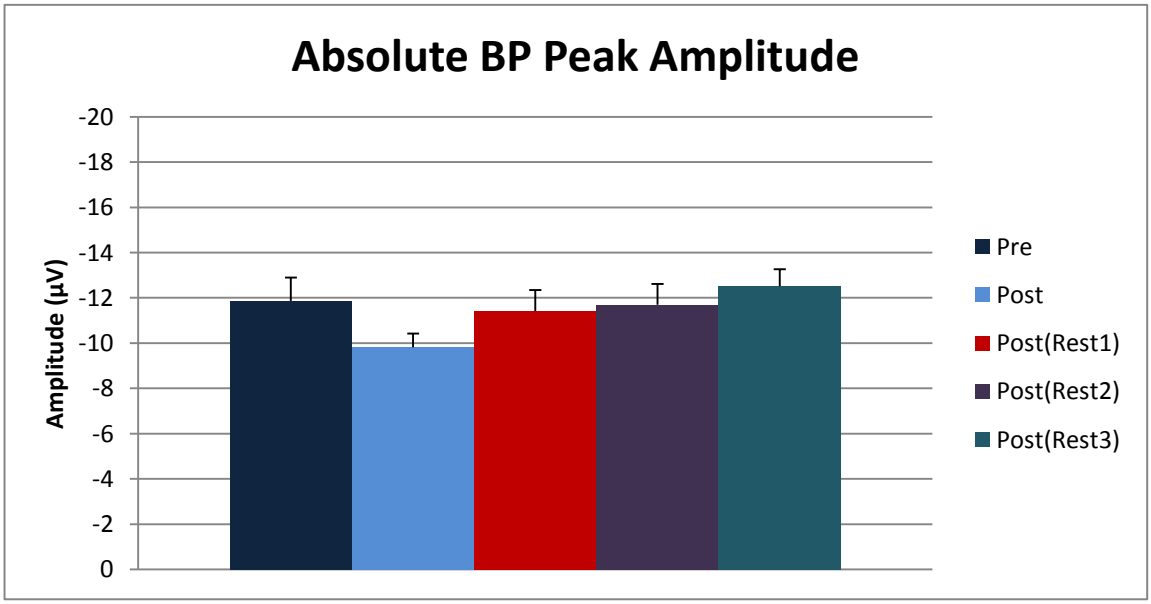


Figure 6b: Average (N=10) absolute peak BP at Cz electrode site across time. Absolute peak BP determined as peak negative deflection between -100 and 200 ms surrounding EMG onset.

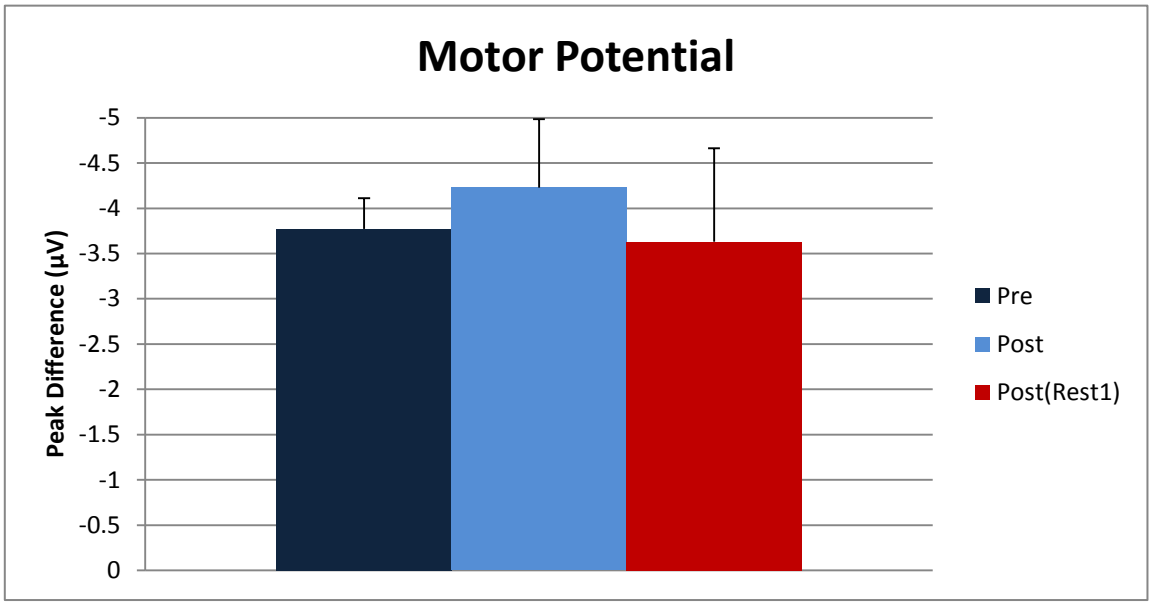


Figure 7a: Average (N=11) motor potential at Cz electrode site across time. Motor potential determined as the difference between absolute peak BP amplitude and the amplitude 150ms prior.

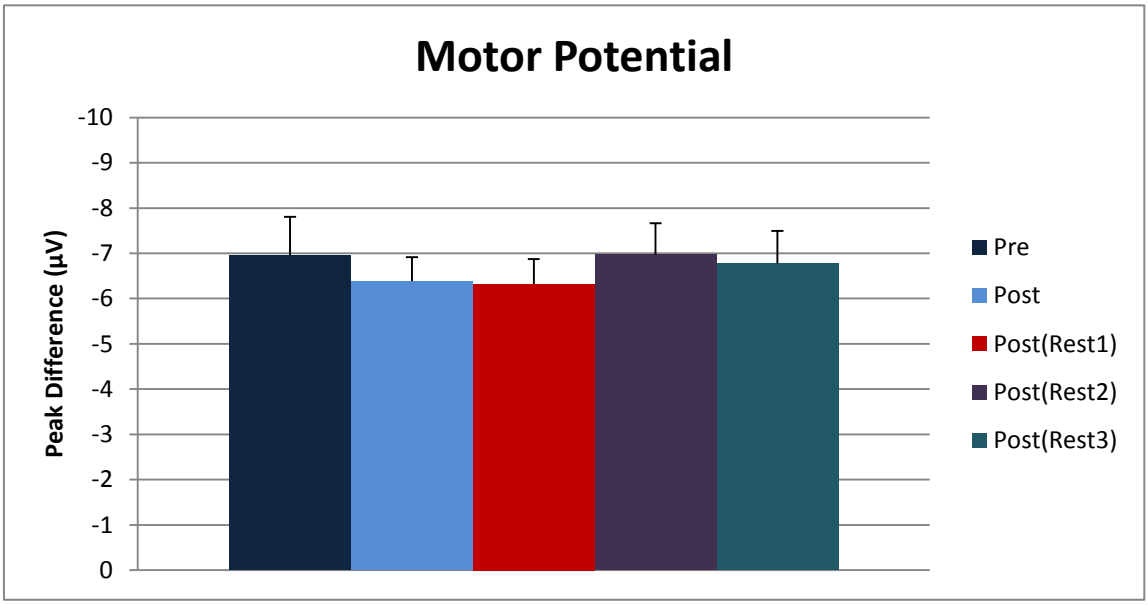


Figure 7b: Average (N=11) motor potential at Cz electrode site across time. Motor potential determined as the difference between absolute peak BP amplitude and the amplitude 150ms prior.

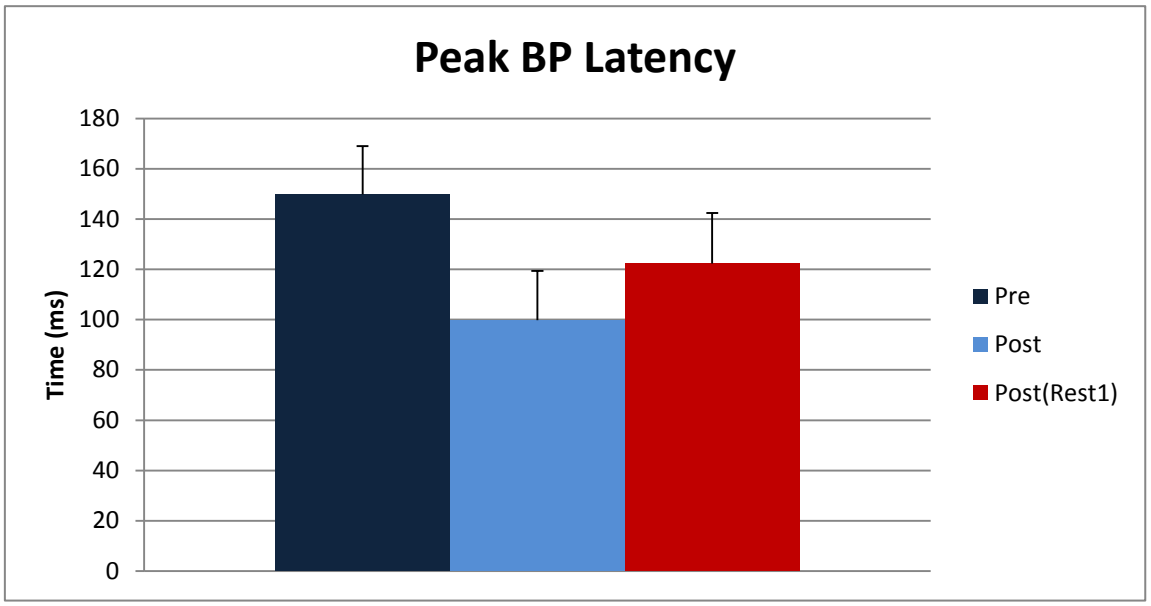


Figure 8a: Average (N=11) Peak BP latency at Cz electrode site across time. Peak BP latency determined as the total time difference between EMG onset and absolute peak BP.

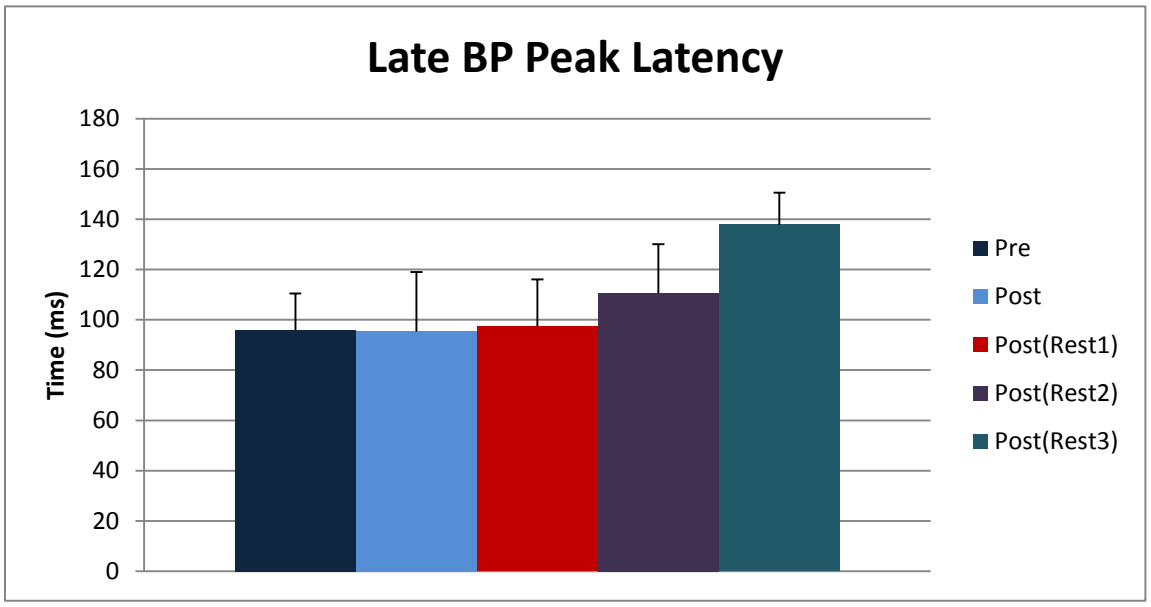


Figure 8b: Average (N=10) Peak BP latency at Cz electrode site across time. Peak BP latency determined as the total time difference between EMG onset and absolute peak BP.

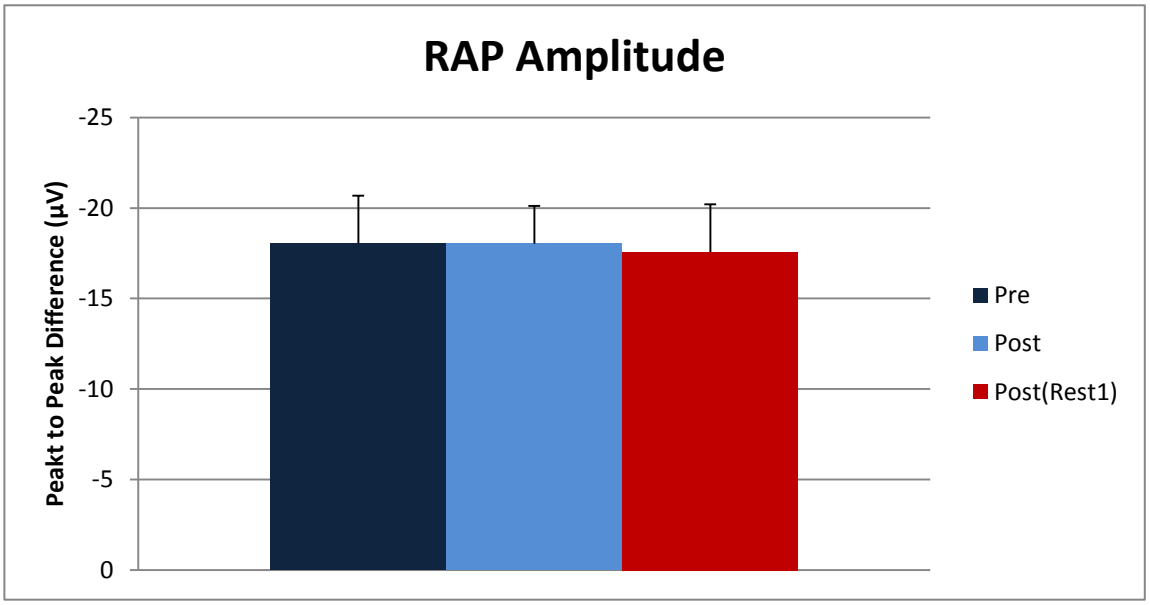


Figure 9a: Average (N=11) RAP amplitude at the Cz electrode site across time. RA P amplitude determined as peak to peak difference between absolute Peak BP and RAP peak. RAP was the absolute positive deflection between 250 and 500 ms after EMG onset.

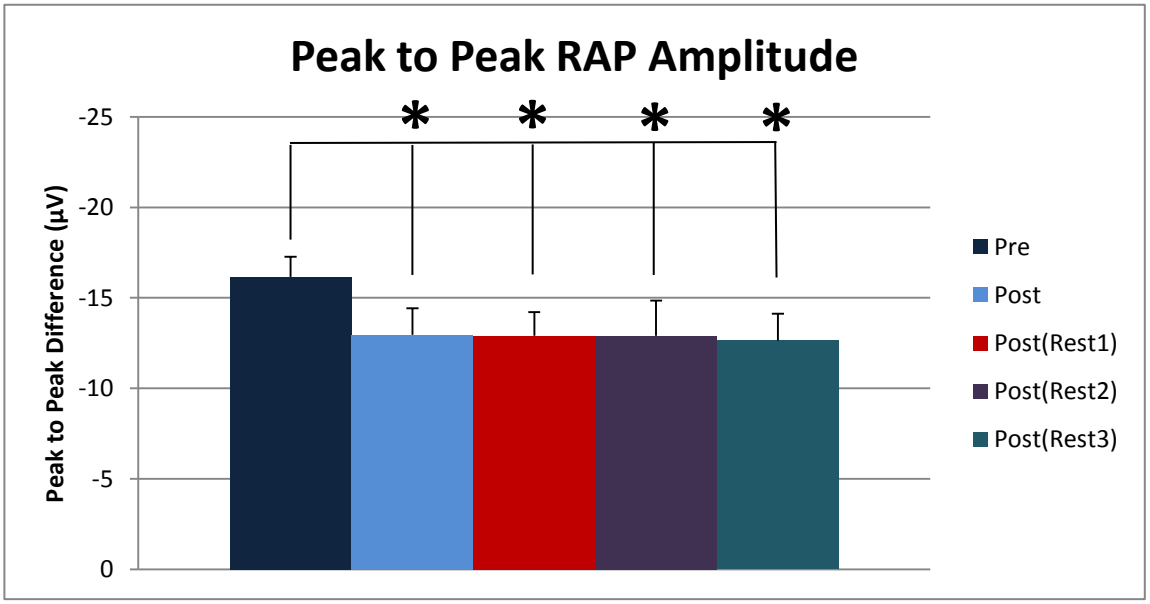


Figure 9b: Average (N=10) RAP amplitude at the Cz electrode site across time. RA P amplitude determined as peak to peak difference between absolute Peak BP and RAP peak. RAP was the absolute positive deflection between 250 and 500 ms after EMG onset.

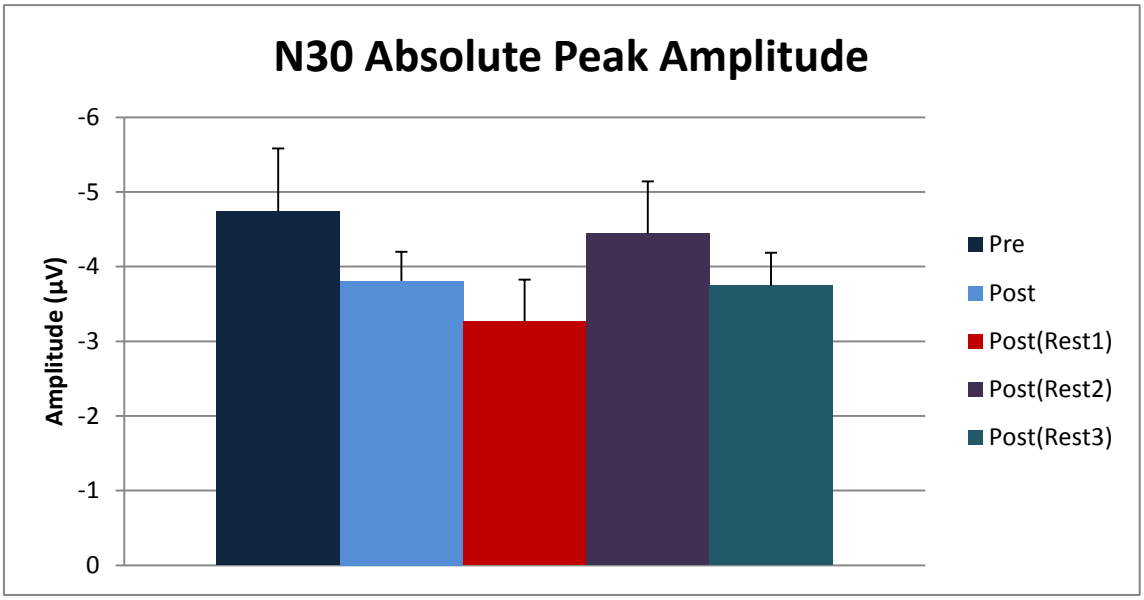


Figure 10a: Average (N=11) N30 peak at Cz electrode site across time. N30 amplitude determined as the greatest negative deflection between 25 and 35 ms after stimulus onset.

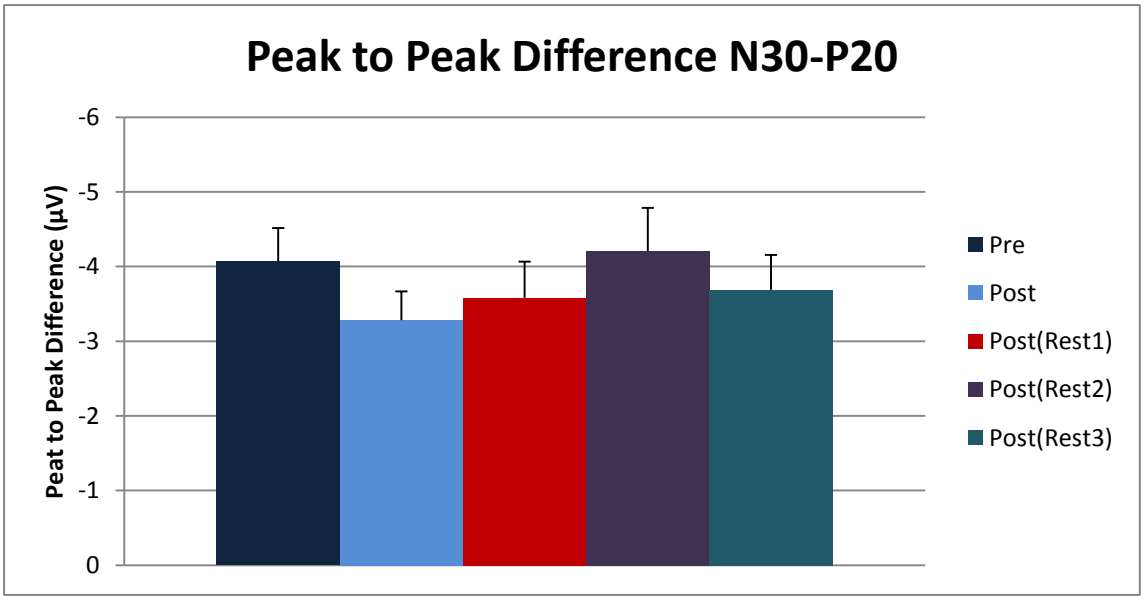
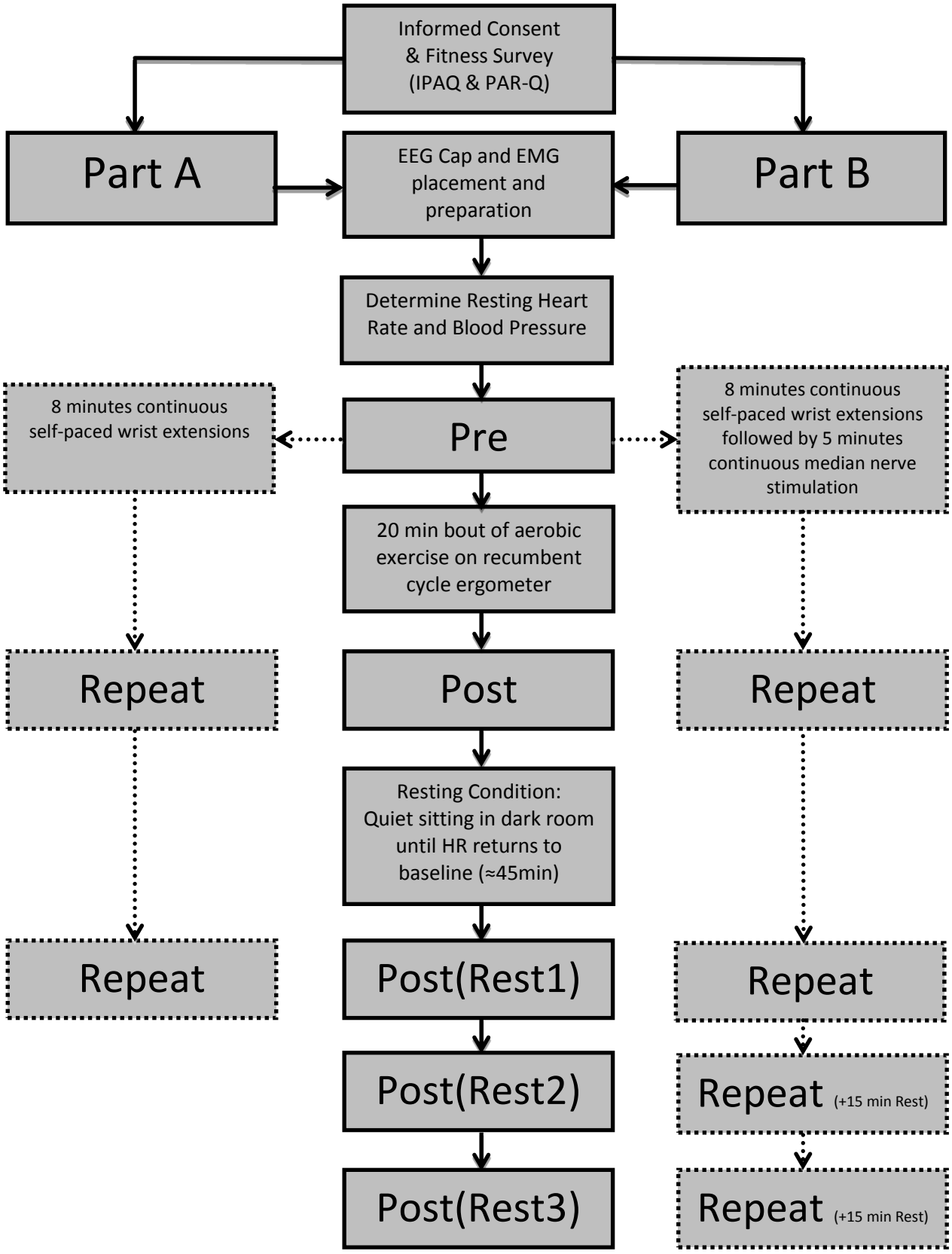
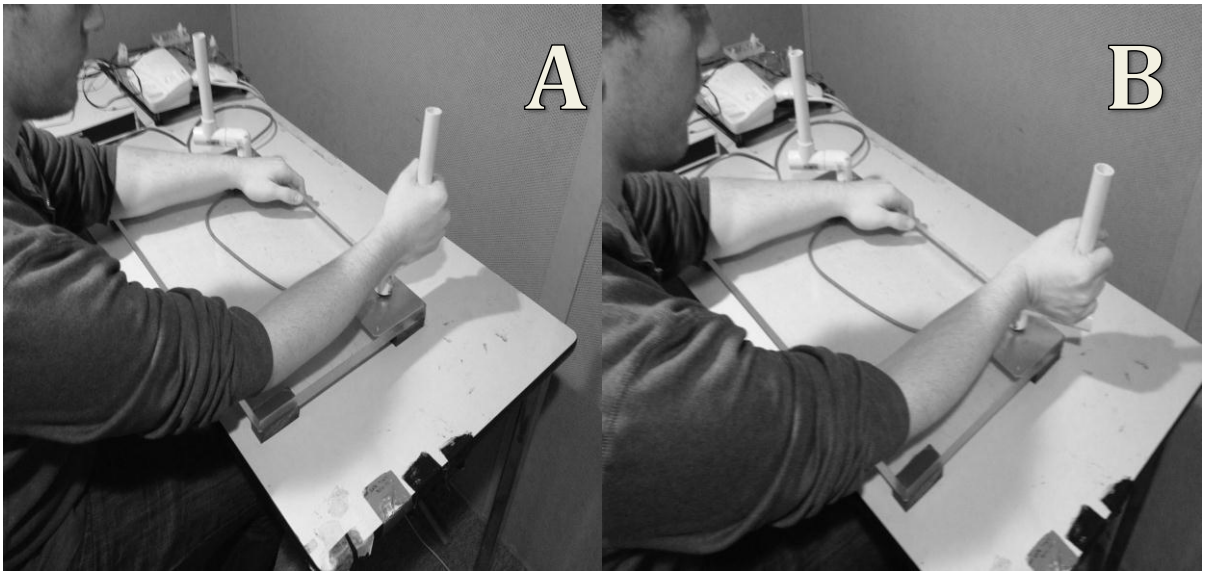


Figure 10b: Average (N=11) N30 amplitude at Cz electrode site across time. N30 and P20 peak determined as the greatest negative and positive deflection between 25 - 35 ms and 18 – 22 ms after stimulus onset respectively. N30 amplitude was determined by peak difference between N30 and P20.

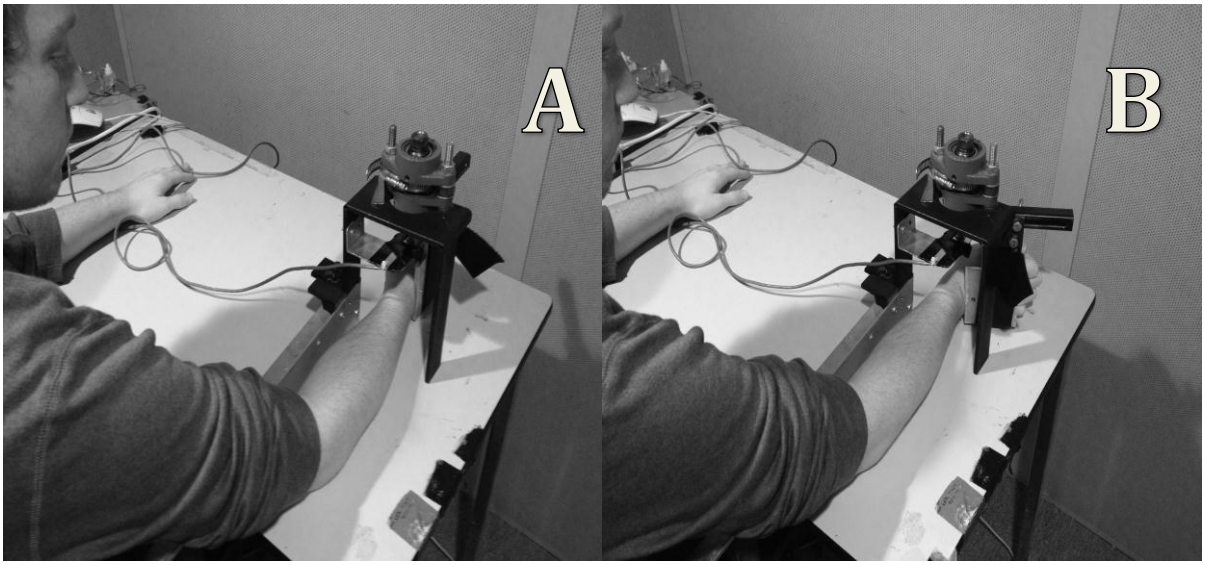
APPENDIX



Appendix Figure 1: Study A & B protocol



Appendix Figure 2: Participant grasping Study A handle apparatus at resting neutral (A) and following self-paced wrist extension.



Appendix Figure 3: Participant bound hand to Study B handle apparatus at resting neutral (A) and following self-paced wrist extension.

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