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WASHINGTON UNIVERSITY IN ST. LOUIS

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# NEUROPHYSIOLOGICAL ADAPTATIONS TO RESISTANCE TRAINING AND REPETITIVE GRAPSING

by

Michael Joseph Falvo

A dissertation presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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**Abstract of the Dissertation**

Perhaps the most prominent feature of the central nervous system is its ability to respond to experience and its environment. Understanding the processes and mechanisms that govern adaptive behavior provides insights into its plastic nature. Capitalizing on this plasticity is of critical importance in response to injury and recovery (35, 106), and the importance of its promotion is increasingly recognized by rehabilitation scientists. Neurophysiological techniques permitting study of cortical function *in vivo* may play a significant role in validating exercise interventions and disease management approaches (14). It may be possible that with these advances we may better understand the relationship between brain function and therapeutic approaches. For this purpose, we present data on both cumulative and acute effects of motor training to better understand adaptive processes.

Neural adaptations accompany resistance training, but current evidence regarding the nature of these adaptations is best characterized as indirect, particularly with respect to adaptation within central or supraspinal centers (56). To this end, we recorded movement-related cortical potentials (MRCP), i.e. electroencephalography (EEG)-derived event-related potentials, in healthy adults prior to and following a program of lower body resistance training. The cumulative effects of nine progressive training sessions resulted in attenuation of relative MRCP amplitudes. We interpreted these findings in terms of neural efficiency such that for the same pre-training load, central effort is diminished post-training. These data demonstrate the impact of cumulative motor training sessions in fostering a reduction in the level of cortical motor activation.

Such a program may be of a particular utility for individuals with limited motor reserves such as those with Parkinson disease (PD).

Although cumulative effects may foster a more efficient cortical network, the acute demands of a training session have received less attention. It is reasonable to assume that the reverse might be expected (i.e. augmented amplitude) during a motor training session, much like the muscular system is taxed during resistance training exercise. At the level of the cortex, neural activity was studied by recording the MRCP during 150 repetitive handgrip contractions at a high intensity. The goal of this work was to examine whether central adaptive processes used to maintain task performance vary as a function of age or PD. We found that for healthy young adults, augmented activation of motor cortical centers is responsible for maintaining performance. However, this was not observed for older adults with and without PD, where minimal changes in cortical activity were observed over the duration of the protocol. Our findings suggest that older adults and those with PD may rely on alternative mechanisms (i.e. mobilization of additional cortical and subcortical structures) to maintain task performance as compared to increasing activity locally as seen with younger adults. Taken together, our work further supports the adaptable nature of the central nervous system. We note in passing the utility of the MRCP paradigm for observing such effects.

**Acknowledgements**

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**Chapter 3:**

## Chapter 1: Introduction

### *Neuroplasticity*

Adaptive alterations can be induced in the central nervous system (CNS) in response to development, pathology, injury, and activity. The latter is particularly attractive to the rehabilitation scientist given the potential to modify neural circuits through experience (i.e. motor skill training, exercise). Adaptation, both acute and chronic, may be brought about through increases in synaptic strength (24), neurogenesis (32), cortical re-mapping (160), and recruitment of novel brain regions (27). Electrophysiological and neuroimaging techniques offer the ability to study the human brain *in vivo* which may enhance our understanding of the relationship between brain physiology and functional outcomes.

The underlying assumption of these techniques is that observable changes in neurophysiology are reflected in changes in motor behavior (14). For example, establishing normal patterns of neural activation (i.e. structures, timing) in healthy populations can serve as a model to which activity patterns of individuals with neurodegeneration or brain injury may be compared. Moreover, neuroimaging may offer the opportunity to monitor recovery as well as ascertain the efficacy of a therapy approach. Insight into the central adaptive processes associated with neuroplastic change may have widespread impact in clinical neurophysiology. To this end, we studied these adaptive processes in the contexts of resistance training and repetitive grasping in health and disease.

### *Movement-Related Cortical Potentials*

Movement-related cortical potentials [MRCP; (82)] are obtained by reverse averaging the electroencephalogram (EEG) with respect to movement onset as an individual performs self-paced movement (149). Therefore, the MRCP is a composite measure of postsynaptic potentials from a large number of cortical pyramidal cells. Due to their perpendicular orientation to the cortical surface, cortical pyramidal cells produce dipolar currents orthogonal to cortical gray matter (147). This, along with synchronous activation of numerous cells, permits an electrical potential to be detected at the scalp in the form of a slow negative wave. This slow wave is suggested to index motor preparation (82) by reflecting facilitation of underlying cortical areas (9); therefore, the MRCP may provide insight into the cortical contribution to movement (132).

Over 40 years ago, Kornhuber & Deecke (82) first identified this pre-movement component and referred to it as the Bereitschaftspotential or readiness potential. Since then, considerable work has been performed to identify the physiological and clinical application of the MRCP, which is underscored by a recent book devoted entirely to this area (77). As reviewed previously (77, 132), the MRCP begins approximately 1.0 – 2.0 s prior to movement onset is maximal at vertex (i.e. midline centro-parietal area) and is symmetrically distributed about that point. Its waveform is characterized as having distinct early and late phases, distinguishable by an increase in the slope (131) which occurs approximately 400 to 500 ms prior to movement onset (e.g. late phase). [Please see Figure 1 for an illustration of this waveform and its components]. Understanding the neural structures that contribute to generation of this cortical activity has been achieved through combination of MRCP recordings with positron emission tomography (PET),

functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) (98). Significant evidence supports bilateral activation of the mesial frontal cortex (e.g. supplementary motor area, SMA) responsible for early phase activity whereas late phase activity is generated by the contralateral primary motor cortex (M1) with somatotopy. The amplitude of the late phase MRCP is correlated with the level of force produced by the muscle, suggesting that cortical motor commands may scale the level of muscle activation (136). Taken together, early and late phases likely represent non-specific preparation (26) as well as specific execution of the movement (50). Secondary to this serial activation (i.e. SMA, M1), descending volleys are sent via the corticospinal tract to produce movement (28, 122). Several additional lines of evidence support decomposition of this waveform into early and late phases.

Given the strong basal ganglia-thalamocortical projections to the SMA, it is not surprising that MRCPs are abnormal in Parkinson disease (PD). [Please see Figure 2 for an illustration of the basal ganglia circuitry]. To this end, a reduced MRCP amplitude in PD is widely acknowledged (114). Specifically, *early* phase activity in those with PD is reduced compared to control subjects (25), which is consistent with the clinical manifestation of bradykinesia, the slowing of movement. However, when patients are provided external cues to initiate movement, their performance is enhanced (78). Touge and colleagues (150) extended these findings in a study comparing two types of self-paced voluntary movement, repetitive forward movement or random-choice. While amplitude of the MRCP increased in healthy subjects for the random-choice movement, no differences were found for those with PD. The authors suggest self-selection processes are abnormal in PD which, combined with results from related studies (30, 78),

supports the hypothesis that provision of external cues may bypass defective basal ganglia circuits.

Although there are data to support distinct contributions to the early and late phase components of the MRCP, it is unlikely that delineations are exact. For example, intracranial recordings have demonstrated consistent SMA activation during the entire time course of the MRCP (75). In addition, segregating these waveforms during data reduction has been performed somewhat arbitrarily, and resulted in the empirical identification of varied and numerous pre-movement components [c.f. Table 1; (132)]. However, several authors have decomposed the MRCP into three main components: the Bereitschaftspotential (BP), motor potential (MP), and movement-monitoring potential (MMP) [(22, 45, 83, 138)]. These components are illustrated in Figure 1 and denote general motor preparation, specific preparation, and motor execution, respectively.

***Cortical Plasticity in Response to Resistance Training***

Exercise training-induced increases in EMG amplitude have been observed in many investigations, but represent only one component of the neural chain of adaptation. Duchateau and Enoka (47) outline a six-component scheme to describe areas of neural adaptation evoked by chronic physical activity, which includes central motor command. Attempts to study central neural adaptation have employed a variety of experimental approaches, including use of evoked responses and cross-education.

Transcranial magnetic stimulation (TMS) applied over the motor cortex produces a motor-evoked potential (MEP), which purportedly offers a method to quantify neural drive to muscle. Changes in MEPs, as detected by surface EMG at the muscle of interest,

reflect only the excitability of the motor cortex which may complicate the interpretation of voluntary drive. In humans, increased excitability has been reported following motor skill training (79), but this has not been found following a resistance training program (21, 79). Some have suggested that adaptations elicited via resistance training are specific to the spinal cord circuitry and are dissimilar to those of motor skill acquisition.

Despite these TMS data (21, 79), many still hypothesize that supraspinal adaptations, occurring with motor skill training, are also likely present with resistance training. The contralateral strength training effect, whereby unilateral training induces strength gains in the contralateral homologous muscles, has been reviewed in detail elsewhere (20, 71). This response appears to be specific to the contraction type performed during training (i.e. specificity), and may even be revealed through imagined contractions (165). This contralateral response is not associated with hypertrophy, but could result from "spillover" of cortical activity to contralateral pathways, and/or adaptations in the control system for the trained ipsilateral limb that may be accessed by the contralateral limb (20). Recently, Farthing et al. (52) reported new activation, detected using fMRI, of the contralateral sensorimotor regions for the untrained limb following unilateral strength training. These findings are the first to provide direct support for supraspinal adaptation as a mechanism for cross-education. In addition, this is the first study to demonstrate cortical activation changes following six weeks of strength training (ulnar deviation).

There is much additional evidence beyond the scope of this review (e.g. motor unit synchronization, evoked spinal reflexes, bilateral deficit phenomenon, transfer of training effect) that is suggestive of supraspinal adaptation. Again, this supportive

evidence for supraspinal adaptation brought about by resistance training is generally obtained from indirect measurement acquired at the periphery and therefore distant from the cortex. Neuroimaging and neurophysiological techniques may circumvent some of these limitations, but have seen infrequent use.

If, secondary to resistance training, individual motor units are capable of producing more force, then fewer motor neurons are required to accomplish a physical task. Presumably, a reduction in recruitment would be reflected in diminished cortical activation. Carroll et al. (21) hypothesized that a reduction in cortical activation would be beneficial in reducing the activation of neural elements unrelated to the intended movement, thereby resulting in enhanced performance. This hypothesis is grounded in observations of increased motor unit synchrony following resistance training (34), as well as cross-sectional data demonstrating greater synchrony in the hand muscles of weight lifters compared to controls (130). Additionally, neuroimaging (e.g. fMRI, PET) studies have demonstrated *reduced* activity at several cortical sites including pre-motor and parietal cortices (73, 153) following motor skill training. Collectively, these data imply resistance training may evoke changes in corticospinal control to enhance efficiency.

Neuroimaging findings appear consistent with EEG studies as well, specifically MRCP paradigms. Those participating in chronic skilled activity, such as rifle shooters pulling the trigger of a rifle, consistently demonstrate decreased MRCP amplitude in comparison to novices (39, 53). These adaptations, e.g. reduced cortical activity, suggest more efficient movement preparation and execution (68). MRCPs are also capable of distinguishing between athletes and non-athletes. Kita et al. (81) reported that the early phase of MRCPs preceding wrist extension were shorter and smaller in athletes (e.g.

kendoists and gymnasts) than in non-athletes. In addition, topographical mapping demonstrated more localized activity in the contralateral motor area in athletes rather than non-athletes. These authors speculate that habitual physical training involving wrist extension has caused diffuse brain activation to become specific.

Several investigations have examined the association between movement kinetics and the components of the MRCP. Siemionow et al. (136) demonstrated MRCPs (e.g. late phase of supplementary- and sensori-motor areas) to be significantly correlated (r = 0.84 – 0.95) with joint force, rate of force development, and muscle activation during elbow flexion exercise. Similar relationships have also been demonstrated in lower extremity (e.g. plantar flexor) movements (44). Presumably, if MRCPs are able to accurately distinguish between force amplitudes and rates (44, 136), as well as athletes and non-athletes (81), the MRCP paradigm may be effective in identifying supraspinal adaptation elicited via resistance training. This approach was undertaken in *Chapter 2*.

***Cortical Plasticity in Response to Repetitive Contractions***

Rodrigues and colleagues (121) recently highlighted that numerous studies have explored the limits of the motor system with finger tapping tasks, but have concentrated predominantly on aspects of motor control, and less so on dynamic changes (i.e. deterioration) in performance over time. As volitional movement necessitates a series of proximal to distal events, each level of the neuraxis may contribute to performance deterioration during repetitive or sustained muscle contractions. Similarly, each level may also contribute to performance compensation. While substantial data are available to support peripheral changes (e.g. metabolic/biochemical changes, motor unit

recruitment and firing rates), significantly less information is available detailing changes higher up the neuraxis (i.e. central adaptations). Several studies (8, 11, 91, 121, 127) support the notion that central adaptations occur in order to maintain motor performance, and it is these adaptations that are the focus of the present work in *Chapter 3*.

In order to study central adaptations, researchers have employed the ubiquitous repetitive handgrip paradigm, designed to be physically demanding. In these studies, participants are asked to perform intermittent or sustained contractions at a certain level of maximal voluntary contraction (MVC). Frequently, TMS has been applied to the cortex prior to and following such a protocol in order to examine changes in cortical excitability via MEPs. Indeed, a number of studies have utilized these methods during repetitive contractions (7, 8, 74, 99, 125, 145, 146); collectively, they have reported modulation of excitatory and inhibitory pathways or increased corticomotor excitability and decreased intra-cortical inhibition, respectively. It is suggested that these adaptations act concurrently to increase central motor drive and maintain task performance.

Central changes in response to submaximal handgrip exercise have also been observed using fMRI and are consistent with augmented central motor drive observed in TMS studies (6, 90, 92). Specifically, during the handgrip protocol an increase in the fMRI signal measured from the contralateral primary sensorimotor cortex was observed. It was suggested that this sign of activation reflected enhanced sensory processing and corticomotor drive in order to maintain task performance (6). A linear rise in the fMRI signal is not confined to primary motor areas but has also been demonstrated in secondary and association cortices (e.g. supplementary motor, prefrontal, and cingulate areas) as well subcortical structures (e.g. cerebellum, cingulate gyrus) (90, 92). Authors

suggest these findings reflect integrated processing of sensory information as well as the brain increasing its output to maintain task performance (92). This recruitment of an extended cortical network is in keeping with the *shifting of activation center hypothesis* whereby if neurons in one location become unable to maintain adequate output, the brain may shift activation to another group of neurons in order to maintain task performance (91). Through EEG source reconstruction, Liu and colleagues (91) were able to demonstrate a shift in the location of the center of cortical activation in response to 200 intermittent handgrip contractions. The authors reasoned this shift represents neural strategies to produce sufficient drive in order to maintain task performance.

Studying central changes in response to repetitive handgrip contractions has also been approached utilizing the MRCP paradigm (57, 80, 93, 127). Similar to TMS and fMRI studies, marked increases in MRCP amplitude are demonstrated over the duration of the handgrip protocol (57, 80, 127). Schillings et al. suggested the extent of MRCP increase reflects compensation by primary motor cortex and supplementary motor area for force-reducing factors (127). Therefore, irrespective of methodology (e.g. TMS, fMRI, or EEG), there appears some consistent evidence regarding central adaptive processes. Also consistent with these studies is the pervasive use of healthy young adults as study participants. Therefore, very little is known regarding adaptive-effects during a repetitive motor task in healthy aging as well as individuals with central activation impairments (e.g. Parkinson disease).

*Voluntary Motor Action in Healthy Aging and Parkinson Disease*

Neuronal processes governing volitional motor action changes with healthy aging (155) and Parkinson disease (PD) (67, 118, 119, 124, 164). As reviewed previously (88, 89), several studies have demonstrated that advancing age is associated with a faster rate of motor progression in individuals with PD. Therefore, it is necessary to understand the independent and interacting effects of healthy aging and PD (72). To this end, a number of neuroimaging studies have been performed comparing brain activity in individuals with PD ('on' and 'off' states) with that of healthy controls. These designs have focused primarily on 'simple' movements such as button presses, finger-thumb oppositions, or joystick movements.

During these simple tasks, neural activity in older adults has been suggested to follow the HAROLD model of cognitive aging (17) whereby there is a reduced lateralization of neural activity. A proposed mechanism for these patterns may be changes in transcallosal inhibitory connections (107), and these phenomena appear to occur gradually across the lifespan (72). In addition to these robust findings, studies have demonstrated specific increases in activity amongst motor and premotor cortices and SMA (100, 107, 156), including evidence of reorganization (e.g. ipsilateral motor recruitment) (107, 156). Although these features of neural activity are well characterized in simple discrete movements, very little is known regarding the dynamic changes over the duration of a motor task (e.g. repetitive grasping).

Several unique patterns characterize neural activity during simple motor actions in individuals with PD. According to classical models of PD (38), basal ganglia dysfunction reduces the excitatory thalamic drive to the cortex by imposing an increased

inhibitory drive on thalamic nuclei. Keeping with this model, dorsolateral prefrontal and medial frontal cortices (e.g. SMA) are impaired during execution of simple movements (43, 124, 164). This impairment is exacerbated in the absence of external cues when movement is self-initiated (78). Strategies of central nervous system compensation in order to maintain task performance have been suggested and are supported by findings of hyperactivation in the primary motor cortex (67, 124, 164), cerebellum (119, 164), and lateral premotor cortex (40, 67, 124). Impairments in task-related activations are attenuated with dopaminergic medication (40, 67, 119) and have been shown to reverse abnormal cortico-motorneuron activity (96). Similar to studies on aging, these findings have not yet been extended to motor paradigms that consider the dynamic aspects of performance (e.g. deterioration with repetition).

To our knowledge, only one study has addressed the independent and interactive effects of aging and PD using fMRI (72). These authors found that aging differentially affected those with PD and controls and interacted with dopaminergic medication (72). In agreement with previous studies, they found aging to increase activity in bilateral motor and premotor regions. In those with PD 'off' their medication, task-related activity increased with age and was similar to controls, except right cerebellar activation which was increased in young patients but declined with age. When tested 'on' their medication, cortical activation (e.g. superior orbital gyrus, anterior cingulate, insula, temporal cortex, and thalamus) was greater in younger patients and declined with age, independent of disease severity. This finding of increased activity in younger 'on' patients was suggested to reflect a greater ability to utilize dopamine for compensatory changes that may not be possible in older patients (72). However, categorical

comparisons of 'on' and 'off' medication therapy were not significant when age was not considered. Collectively, these studies suggest clear differences between healthy aging and PD which underscore the influence of age.

***Summary***

Cortical properties of the human brain maintain the ability to adapt throughout the life span, and these changes likely comprise the basis of learning and recovery (13). Recent advances in technology have prompted novel investigations permitting *in vivo* examination of the evolution of brain activity which has the potential to shape and guide clinical practice (14). Capitalizing on the assumption of a relationship between motor behavior and brain activation, important distinctions may be made. These include identifying categorical differences (i.e. effects of aging, neurodegeneration) in neural activity during performance of a motor task, and determining the efficacy of an intervention. To this end, we have studied how the cortical motor system responds cumulatively to motor training (*Chapter 2*) as well as acutely to a progressive motor task (*Chapter 3).*

**Figure 1:**

Measurement windows of the movement-related cortical potential (MRCP): Bereitschaftspotential (BP), motor potential (MP), and movement-monitoring potential (MMP).

*Note*: The time of '0' on the x-axis indicates movement onset.

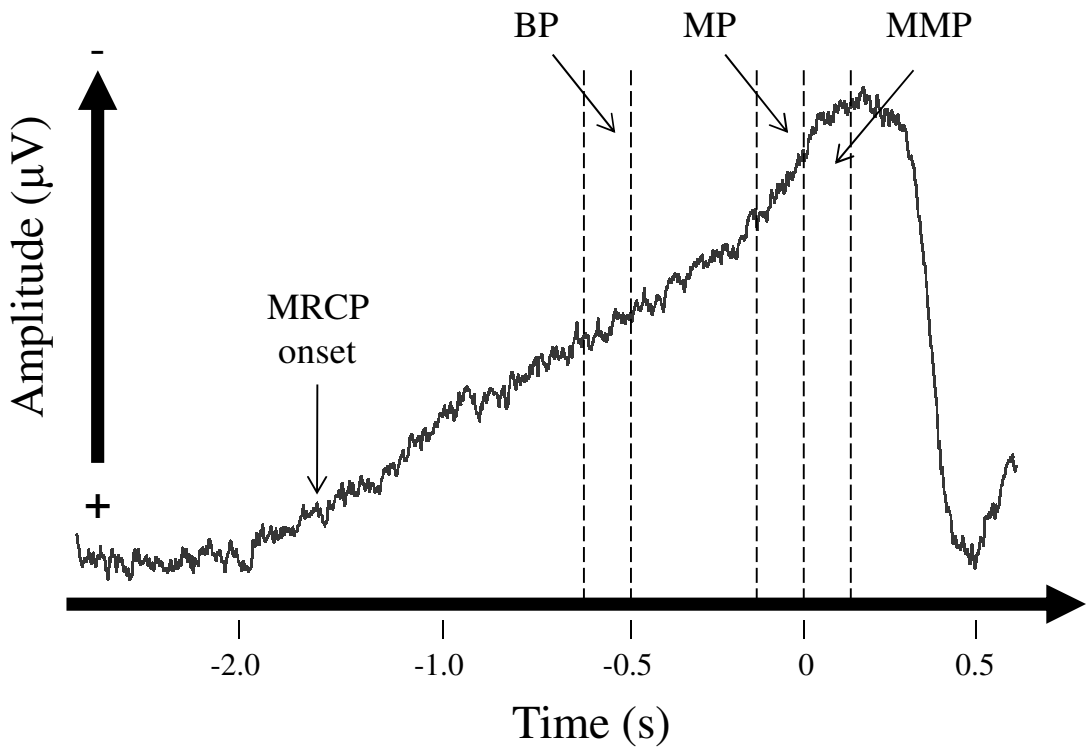
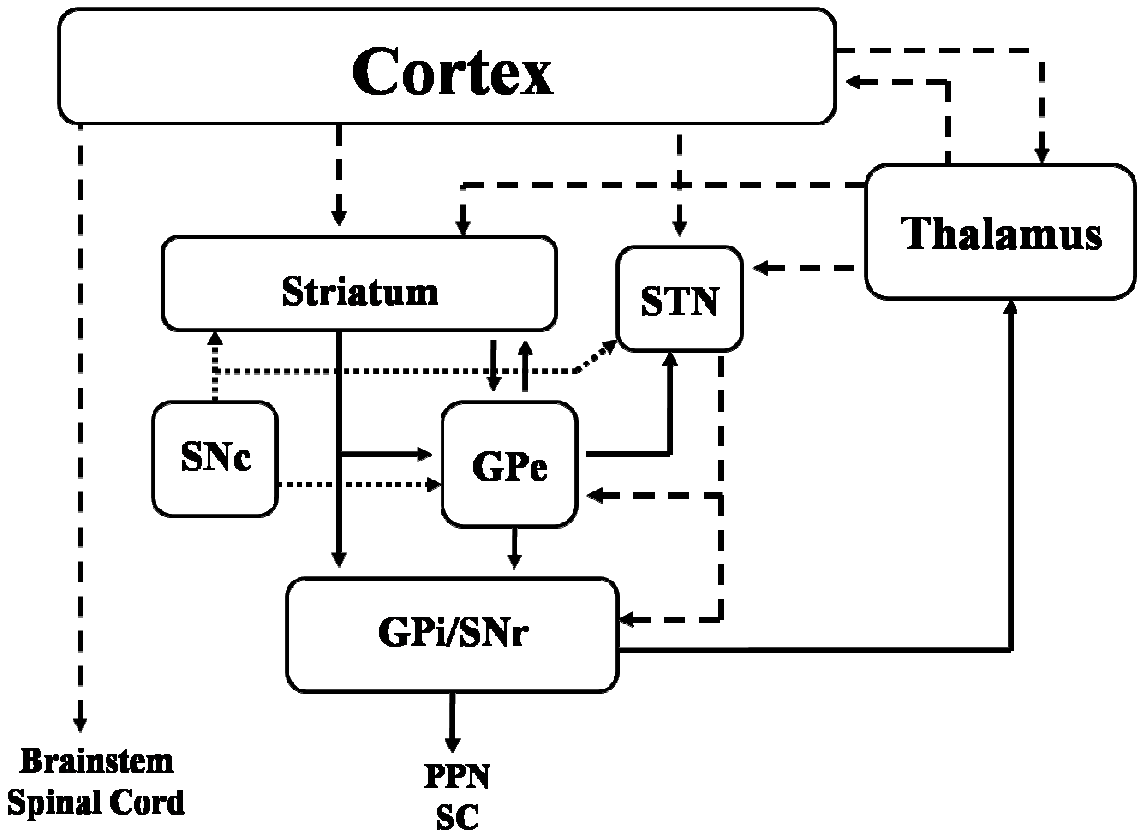

BP
MP
MMP
-
+
Amplitude (μV)
MRCP
onset
-2.0
-1.0
-0.5
0
0.5
Time (s)

**Figure 2:**

Circuit diagram of the basal ganglia. Basal ganglia structures are shaded and include: striatum, internal (GPi) and external (GPe) segments of the globus pallidus, substantia nigra pars compacta (SNc) and reticulata (SNr), and the subthalamic nucleus (STN). Through GPi and SNr, the basal ganglia output to the thalamus, pedunculopontine nucleus (PPN), and the superior colliculus (SC). GABAergic, glutamatergic, and dopaminergic projections are represented by solid, dashed, and dotted lines, respectively.


Cortex
Thalamus
Striatum
STN
SNc
GPe
GPi/SNr
Brainstem
Spinal Cord
PPN
SC

## Chapter 2:

## Resistance training induces supraspinal adaptations: Evidence from movement-related cortical potentials

**Abstract**

Early effects of a resistance training program include neural adaptations at multiple levels of the neuraxis, but direct evidence of central changes is lacking. Plasticity exhibited by multiple supraspinal centers following training may alter slow negative electroencephalographic (EEG) activity, referred to as movement-related cortical potentials (MRCP). The purpose of this study was to determine whether MRCPs are altered in response to resistance training. Eleven healthy participants (24.6 ± 3.5 yr) performed three weeks of explosive unilateral leg extensor resistance training. MRCP were assessed during 60 self-paced leg extensions against a constant nominal load before and after training. Resistance training was effective ($P < 0.001$) in increasing leg extensor peak force (+22%), rate of force production (+32%) as well as muscle activity (iEMG; +47%, $P < 0.05$). These changes were accompanied by several MRCP effects. Following training, MRCP amplitude was attenuated at several scalp sites overlying motor-related cortical areas ($P < 0.05$), and the onset of MRCP at the vertex was 28% (561 ms) earlier. In conclusion, the three week training protocol in the present study elicited significant strength gains which were accompanied by neural adaptations at the level of the cortex. We interpret our findings of attenuated cortical demand for submaximal voluntary movement as evidence for enhanced neural economy as a result of resistance training.

## Introduction

Plasticity and adaptation of the human motor system in response to resistance exercise has been well documented [for reviews: (1, 56, 58, 63)]. The loci of these adaptations are not restricted; rather they appear diffuse throughout all levels of the neuraxis (47). At the level of the motor unit, resistance training has been shown to enhance recruitment, firing rate, synchrony, and the incidence of doublets (152). These observations may be a function of augmented volitional drive along the corticospinal pathway (2, 36, 48) which, in turn, may be preceded by increased cortical excitability (64). Several attempts have been made to link training-induced plasticity in corticospinal pathways to increased force output [c.f. Fig. 8 (36); Fig. 1 (47); Fig. 4 (4)], yet the supporting evidence comes largely from data obtained via peripheral measures (e.g. surface electromyography) which may not adequately reflect changes in supraspinal centers. Consistent with the limited character of existing evidence, the significance and presence of supraspinal adaptation has been questioned, particularly in the early stages of a program of resistance training (21, 79).

Neural adaptations in response to resistance training may be reflected in coordination and learning which act to facilitate recruitment and activation of muscles engaged in a strength task (56). Individuals may 'learn' to increase maximal force output as a form of motor learning (64), and therefore exhibit plasticity in motor cortical areas. Indirect support for supraspinal adaptation comes from studies reporting increased strength gain as a result of imagined contractions (117, 135, 165), cross-education or contralateral strength training effect (3, 52, 86, 105) as well as specificity of training (47). Although direct evidence of modified central motor activity influencing these phenomena

is lacking, supporting evidence can be adduced from investigations that have utilized evoked reflex (H-reflex) and motor evoked potential (MEP) paradigms demonstrating such an effect.

Presumably, the H-reflex, the electrical analog to the stretch reflex, provides a means to assess net synaptic input (e.g. afferent and descending) as well as excitability of the α-motor neuron pool *in vivo* (103). Additionally, the electrophysiological variant of the H-reflex (V-wave), obtained through supramaximal stimulation of a mixed nerve, has been used to assess the magnitude of efferent neural drive in descending corticospinal pathways (2). When combined, the H-reflex and V-wave may provide estimates of spinal and supraspinal adaptations, respectively. Facilitation of the H-reflex has been observed following short-term plantar flexor resistance training in some (70, 86), but not all experiments (36, 48, 55, 62). In those studies unable to elicit changes in H-reflex amplitude (i.e. spinal excitability), increases in evoked V-wave responses were reported, suggesting an augmented volitional drive via supraspinal adaptation (36, 48, 55, 62). Lack of consistency amongst these studies may reflect limitations of the H-reflex measure, which has been shown to be highly modifiable and influenced by a variety of factors (103).

MEPs elicited via transcranial magnetic stimulation (TMS) have been used to examine the neural adaptive effects of resistance training in three separate investigations with equivocal results. Following four weeks of isometric tibialis anterior training MEP amplitude increased by 32% (64), but a depression in cortical excitability was noted for training of the biceps brachii (79) and first dorsal interosseous (21). Griffin and Cafarelli (64) suggested that these differences may lie in the differing responses of certain muscle

groups to TMS and/or dissimilar training protocols. Moreover, changes in the excitability of cortical, subcortical, or spinal neurons likely influence the TMS-induced MEP as the rise time is long enough to include multiple pathways (144). For example, alterations at the spinal level (e.g. recruitment, rate coding, synchronization) could potentially influence the evoked force induced by TMS (37).

An alternative to evoked responses which does not introduce artificial input to the central nervous system or involve the recording of responses distant from the cortex (e.g. surface EMG) (127), may be better-suited for detecting supraspinal adaptations secondary to resistance training. Surface negative potentials, detected at the scalp via electroencephalography (EEG) around the time of voluntary movement, are referred to as movement-related cortical potentials (MRCP). MRCP reflect the summed excitatory post-synaptic potentials of apical dendrites and are related to the preparation and execution of self-initiated movement [for review: (132)]. It is generally agreed that the temporal course of the MRCP waveform shows an onset 1 – 2 s prior to movement onset bilaterally in the supplementary motor area (SMA), followed by activity in contralateral premotor and motor cortices with a scalp representation that is somatotypically appropriate (132). As a result, MRCP may be delineated into three consecutive pre-movement periods (83, 139), referred to as 1) the Bereitschaftspotential (i.e. preparation), 2) motor execution and 3) movement-monitoring potentials. The amplitude of each component is a function of the number of active neurons, their synchrony and rate of discharge (136). The later MRCP components have been correlated with force, rate of force development, and associated EMG amplitude for both elbow-flexion (136), and

plantar-flexion movements (44) suggesting that MRCP may index the level of muscle activation.

The present study investigated the possible involvement of supraspinal adaptations in resistance training, using MRCPs as a measure of brain activity. We have noted above several attractive aspects of the MRCP method in this context, including their spatiotemporal resolution and known origins in the underlying cortices. Specifically, we hypothesized that strength training would allow the motor tasks to be performed with less relative effort resulting in adaptive changes in MRCP related to enhanced neural efficiency. The present experiment is, to our knowledge, the first to utilize EEG (e.g. MRCP) as a tool for examining plasticity of the central nervous system in a resistance training paradigm.

## Materials and Methods

*Subjects and Design.* Eleven healthy volunteers (9 women; 2 men), with a mean age of 24.6 ± 3.5 yr and body mass of 63.8 ± 9.2 kg, participated in this investigation. All participants were right hand and foot dominant, as assessed through self-report, and had not participated in any resistance training for at least the past year. Participants had no known history of musculoskeletal injury or neurological events, and were deemed eligible to participate in resistance exercise by the Physical Activity Readiness Questionnaire [PAR-Q; (148)]. Following a detailed verbal explanation of study procedures, participants provided their written informed consent and were then familiarized with the training and testing equipment. The Washington University School

of Medicine Human Research Protection Office approved the experimental procedures, which were in accordance with the Declaration of Helsinki.

To control inter-individual variance in the MRCP response, this study employed a quasi-experimental (i.e. pre/post) design where participants served as their own controls. Each participant participated in two experimental sessions separated by a three-week resistance training period. During each experimental session, participants performed maximal and submaximal leg extensions of the dominant leg. Maximal voluntary isometric contractions were performed first, followed by 60 submaximal repetitions. EEG data were recorded only during the submaximal repetitions, whereas force and EMG data were recorded during maximal and submaximal performance. Prior to the training intervention, a subset of subjects (N = 7) also completed a second pre-test session within three to seven days of their first in order to confirm test-retest reliability of the MRCP measures. All participants completed their post test between 1 to 3 days following their final training session.

*Apparatus*. Participants performed unilateral maximal and submaximal leg extensions on a modified leg press device (Champion Barbell; Dallas, TX) instrumented with four load cells (Transcell Technology Inc.; Buffalo Grove, IL) which were encased within the foot plate (Fig 3). A custom-built mechanism was attached to the device that allowed 2 cm individual adjustments. These adjustments were made, and were reproduced for post-testing, such that each participant was positioned in a recumbent seated position in 110° of hip flexion. Locking of this mechanism enabled maximal isometric testing, but could be released for the submaximal MRCP protocol. When

released, the leg press device became freely moveable and although no external weight was added, the device itself produced a constant load of approximately 18 kg.

*Electrophysiological recordings.* Participants were fitted with either an appropriately sized 61-channel elastic nylon Quick-cap (Compumedics; Charlotte, NC), and EEG data were acquired using the 70-channel Synamps2 amplifier system and recorded in the Acquire module of Scan 4.3 (Compumedics; Charlotte, NC). This system has a common mode rejection ration of 100 dB, 24-bit A/D resolution, and input impedance of 10 MΩ. Data were recorded with a bandwidth of DC-100Hz and sampled at 1KHz. Impedances were kept below 5 kΩ for all electrodes.

Vertical and horizontal electrooculograms (EOG) were recorded using Ag/AgCl electrodes placed above and below the right eye and the left and right outer canthi, respectively. Electromyographic activity (EMG) of the vastus lateralis was recorded from bipolar electrodes with an inter-electrode distance of approximately 20 mm. Electrodes were arranged according to Surface ElectroMyography for the Non-Invasive Assessment of Muscles (SENIAM) (69) recommendations. Prior to electrode application, the skin was cleaned and vigorously abraded. EOG, EMG, EEG and force signals were all continuously and synchronously recorded through the Synamps2 amplifier and Scan 4.3 software.

*Resistance training.* Supervised unilateral training of the leg extensors was conducted three times per week on non-consecutive days for three weeks (i.e., nine total sessions). A relatively brief, three week training regimen was selected on the basis of evidence that neural plasticity governs early adaptive effects (70). In addition, leg extensions were performed explosively in order to maximize neural adaptations (5, 65,

152). Participants were encouraged to maximally accelerate the load in the concentric phase and slowly (e.g. 2 s tempo) return the load in the eccentric phase. All training was progressive in nature as volume and intensity increased after the third and sixth sessions. Initial training loads were based upon one-repetition maximum (RM) strength, which was determined prior to the first training session. Sessions 1-3 consisted of three sets of 10 – 12 repetitions at 70-75% RM; Sessions 4-6 consisted of four sets of 8 – 10 repetitions at 75-80% RM; Sessions 7-9 consisted of five sets of 6 – 8 repetitions at 80-85% RM.

*Strength and muscle activity assessment.* Maximal voluntary isometric contraction (MVIC) of the dominant leg extensors was determined from three separate maximal attempts in which subjects were instructed to contract as hard and as fast as possible and to maintain the contraction until they were instructed to release (~ 3 s). MVICs were preceded by several submaximal preconditioning contractions and a rest period. Force signals and concomitant EMG of the vastus lateralis were synchronously sampled at 1KHz and digitally converted as described earlier.

Offline, the summed force signals were digitally smoothed using a $4^{th}$ order, zero-lag Butterworth filter (15 Hz cutoff). Force-time histories were analyzed for MVIC and the rate of force development (RFD). Maximal RFD was computed as the highest values of the slope coefficients of the tangent computed during a sliding 5 ms window (154). Onset of contraction was detected using a threshold criterion of 5 Newtons and was confirmed with visual inspection. The average of three MVIC attempts was used for statistical analysis.

Raw EMG signals were digitally high-pass filtered using a $4^{th}$ order, zero-lag Butterworth filter (5 Hz cutoff), and followed by a moving root-mean-square filter with a

50 ms time constant (2). Onset of EMG was defined as the moment preceding the onset of contraction by 70 ms to account for the presence of electromechanical delay (2). Variables of interest included peak EMG during contraction ($EMG_{pk}$), and the average integrated EMG in the 200 ms time interval prior to peak force ($EMG_{200}$) as described elsewhere (85). Force and EMG signal processing was performed using Datapac 2K2 software (v3.16; Mission Viejo, CA).

*MRCP acquisition and analysis.* Following MVIC testing and a 5 min rest period, each participant performed three sets of 20 self-paced leg extensions of the dominant leg. Interspersed rest periods of approximately 5 min were given to minimize possible physical and mental fatigue. Participants started from an initial position of 110° hip flexion and 80° knee flexion. (See Fig 3) Upon completion of the movement, they reached a position of 70° hip flexion and 0° knee flexion. Participants were instructed to briskly extend their leg during the concentric phase then slowly lower the arm of the leg press to the starting position (i.e. eccentric phase). Prior to commencing subsequent repetitions, participants were instructed to relax and wait calmly for at least 5 s. To minimize the influence of eye movements on the EEG signal, participants were instructed to maintain an open-eye, fixed-gaze on a target located approximately 3 m in front of them. They were also told to refrain from tensing muscles other than the involved leg extensors and to avoid eye blinks in the period before and during the leg extension to avoid generating artifacts. Their arms gently rested on handles attached to the seat of the leg press device. Between trials (i.e. repetitions), eye blinks were allowed as these periods were not included in the triggered averaging.

All offline analysis was performed utilizing custom MATLAB programs (v7.3.0; Math Works, Inc.; Natick, MA). Raw EEG data were inspected visually to identify and remove artifacts. Trials containing blink artifacts occurring during epochs of interest were excluded. Data were high-pass filtered at 0.01 Hz (90 db) to eliminate the baseline shift generated by DC recording and were referred to a common average. For each trial, the onset of force was used to synchronize a 4 s epoch, 3 s before the onset and 1 s after onset. Force onset was defined as the point when the force signal exceeded a threshold of two standard deviations above the activity level at the beginning of the epoch and subsequently remained above that level for at least 500 ms. Non-contaminated epochs were averaged together forming an average MRCP for each participant.

MRCPs were decomposed into three distinct components (83, 138): 1) mean amplitude between -600 and -500 ms prior to movement onset, or *Bereitschaftspotential* ($BP_{-600\ to\ -500}$), 2) mean amplitude between -100 ms and movement onset, or *motor potential* ($MP_{-100\ to\ 0}$), and 3) mean amplitude from onset to +100 ms, or *movement-monitoring potential* ($MMP_{0\ to\ 100}$). Amplitudes were computed with reference to a baseline of -3500 to -3000 ms prior to movement onset. Latencies were also determined by computing the time interval from onset of MRCP negativity to force onset. Onset of negativity (i.e. MRCP onset) was identified as the point when the baseline signal deviated from a 95% confidence interval and subsequently remained above that level for at least 500 ms (159) from the period of -2500 to -2000 ms preceding movement. Analysis focused primarily on three central electrode sites: Cz, C1, and C2. These sites were chosen because leg movements are associated with high activity over the supplementary motor area and demonstrate bilateral motor cortex activation (97).

Also in each trial, the EMG signal was processed in the same manner as performed in MVIC, but was averaged over a 2500 ms epoch (e.g. 1000 ms prior to 1500 ms after movement onset), and then averaged over all trials. Mean amplitude and onset relative to movement onset (i.e. force onset) were calculated. The criteria for EMG onset were equivalent to MRCP onset described above. Mean force and maximal RFD were obtained by triggered averaging as well.

Two-dimensional (2D) topographical maps were created to reflect spatial features of the MRCP considering the entire 61-electrode montage (Fig 4). Separate 2D maps were created for each of the three distinct MRCP components for pre- and post-testing, using group mean data. Group mean data rather than single-subject data were used to better demonstrate true cortical activity preceding movement (50).

*Statistical analysis.* Paired *t*-tests were used to compare force, EMG, and MRCP measures between pre- and post-tests. As multiple electrode sites were compared, we additionally performed a Hotelling $T^2$ test to maintain statistical power, as has been used previously in similar studies (50). For MVIC measures one-tailed tests were performed to compare force and EMG as these measures are known to increase with resistance training. Two-tailed tests were used to examine MRCP measures. Pearson correlation coefficients were computed to assess the relationships between MRCP measures and force and EMG during the submaximal protocol. Test-retest reliability was assessed via intraclass correlation coefficients ($ICC_{3,1}$) (158) and ICCs greater than 0.60 were considered acceptable (23). Data are presented as means ± SD and statistical significance was set at $\alpha \leq 0.05$.

**Results**

*Reliability.* ICCs for each MRCP measure all exceeded the 0.60 criterion for acceptability as follows: $BP_{-600\ to\ -500} = 0.77$, $MP_{-100\ to\ 0} = 0.82$, $MMP_{0\ to\ 100} = 0.89$, onset latency = 0.92. No significant differences were observed between sessions for any of these measures across electrode sites ($P > 0.05$).

*Maximal strength assessment.* After three weeks of strength training, MVIC increased significantly by 21.6% from 1479.6 ± 579.2 to 1800.0 ± 533.6 N ($P < 0.001$). RFD also significantly increased by 31.6% from 5.3 ± 2.3 to 7.0 ± 2.6 N/ms ($P < 0.001$). In regards to EMG, no difference was found for $EMG_{pk}$ ($P = 0.23$), but a significant 47.2% increase was observed for $EMG_{200}$ ($P = 0.04$).

*Submaximal leg extension performance.* After rejection of contaminated epochs (approximately 35% of trials), the average number of trials analyzed per subject was similar for pre- (34.2 ± 10.8) and post-tests (35.5 ± 12.5). Previous research has demonstrated that the MRCP is associated with the rate and magnitude of force production (44, 136, 138); therefore, these variables before and after training were analyzed to assess their possible contribution to any MRCP effects. Overall, the findings indicated little if any change in submaximal force production. No differences ($P > 0.05$) were observed for mean force (Pre: 277.4 ± 35 N; Post: 282.9 ± 22 N) or RFD (Pre: 2.6 ± 1 N/s, Post: 2.2 ± 1 N/s). Mean inter-trial response interval, defined as the interval between the offset and onset of force production, were also similar between sessions before and after training (Pre: 12.2 ± 1.7 s; Post: 11.4 ± 2.4 s). Similarly, mean EMG amplitude (Pre: 366.6 ± 186.2 μV; Post: 378.4 ± 241.4 μV) and the onset of EMG (Pre: -184.2 ± 93.9 s; Post: -168.91 ± 90.7) were not significantly different ($P > 0.05$).

*MRCP parameters*. MRCP amplitude measures for Cz, C1, and C2 are illustrated in Figure 5, and the waveforms on which these measures are based are illustrated in Figure 6. Irrespective of measure, amplitudes generally were attenuated following resistance training at each of the electrode sites. However, these differences were statistically significant only for $MP_{-100\ to\ 0}$ and $MMP_{0\ to\ 100}$, as $BP_{-600\ to\ -500}$ did not satisfy the Hotelling $t^2$ test ($P = 0.09$). Our automatic detection methods did not consistently detect MRCP onsets at the C1 or C2 electrode sites, therefore latencies were computed only for Cz. A significant difference ($P = 0.02$) was observed for onset latency (Pre: -1939.9 ± 658.3; Post: -1378.2 ± 600.5), such that onsets, on average, began approximately 28% later at Cz after training. Visual inspection of the 2D topographical maps (Figure 4) further confirms the attenuation of cortical activity during each of the three MRCP components. Note statistical analysis was not performed on these maps, which are used for the purposes of illustrating in general form the spatial features and to confirm that the C1-Cz-C2 chain is an appropriate zone for measurement.

No significant correlations were observed for the pre-testing session between MRCP measures and mean force or RFD ($P > 0.05$). However, mean EMG amplitude was significantly associated with $MP_{-100\ to\ 0}$ ($r = 0.68$; $P = 0.03$) and $MMP_{0\ to\ 100}$ ($r = 0.64$; $P = 0.05$), but only at electrode site C2. For post-testing, $MMP_{0\ to\ 100}$ at Cz was significantly correlated ($r = 0.61$; $P = 0.05$) with mean force. No other significant associations were observed for RFD or mean EMG amplitude during the post test.

## Discussion

We hypothesized that following a brief program of resistance training, supraspinal adaptive changes would be reflected in the MRCP. As expected, this 3-wk program elicited marked increases in MVIC, RFD, and $EMG_{200}$ during maximal leg extensor contraction. For repetitive submaximal leg extensions, we observed attenuation of MRCP amplitude at several motor electrode sides, supporting our hypothesis that by increasing strength, comparable motor tasks may be performed with a lower level of neural effort.

We are confident that the observed changes were not artifactual in nature for two main reasons. First, we were able to demonstrate that MRCP are repeatable (ICCs = 0.77 – 0.92) for self-paced submaximal leg extensions, and without intervention, there were no changes in response amplitude measures or onset latencies as seen with our sub-group analysis. Second, we found no differences in the manner in which leg extensions were performed (e.g. force applied, RFD, inter-trial interval) as well the number of trials analyzed before and after training. In concert with the findings of significant differences in the associated MRCPs, these results indicate that MRCP may be a valuable method for evaluating adaptive neural changes in response to resistance training.

*Implications for reduced cortical activity.* If, secondary to resistance training, individual motor units are capable of producing more force, then fewer motor neurons are required to accomplish a given physical task. Presumably, a reduction in recruitment would be reflected in diminished cortical activation. Carroll et al. (21) hypothesized that such a reduction would reduce activation of neural elements unrelated to the intended movement, thereby resulting in enhanced performance. As such, enhanced performance

is likely to reflect a lower metabolic cost, as has been reported elsewhere. For example, elite rifle shooters consistently demonstrate decreased MRCP amplitude in comparison to novices (39), suggesting more efficient movement preparation and execution (68).

Such findings are consistent with results from the present study indicating that the amplitudes of later components, $MP_{-100\ to\ 0}$ and $MMP_{0\ to\ 100}$, were considerably reduced (effect sizes: 0.70 – 0.85) following three weeks of resistance training. It has previously been reported that these same time intervals (e.g. $MP_{-100\ to\ 0}$ and $MMP_{0\ to\ 100}$) are sensitive to inertial loading, whereby amplitudes are greater at appropriate electrode sites when loading is higher (83). In other words, when individuals were asked to perform muscle contractions under light- and heavy-loads, larger $MP_{-100\ to\ 0}$ and $MMP_{0\ to\ 100}$ responses (i.e. greater negativity) were observed under heavy-loading conditions. We consider these findings directly applicable to the present study in which subjects performed movements at a constant load prior to and following resistance training. At baseline, $MP_{-100\ to\ 0}$ and $MMP_{0\ to\ 100}$ amplitudes were 26.1 – 49.7% higher than after training. Since subjects experienced significant gains in MVIC (+21.6%) and RFD (31.6%), it is reasonable to assume that strength gain altered the level of relative loading in which the constant load became lighter after training and thus easier to perform. This is further confirmed by Slobounov et al. (138) who reported MRCP amplitudes to proportionally increase as a function of perceived effort on the part of the subject.

In a cross-sectional study, the MRCP preceding wrist extensions was compared in athletes (e.g. kendoists, gymnasts) versus non-athletes (81). The authors reported that the early component (e.g. BP) in athletes had a later onset and reduced amplitude in comparison to non-athletes. Similarly, we observed that the onset of negativity at

electrode site Cz occurred on average 561 ms later following training (Fig 6). However, we did not find a significant decrease in amplitude at $BP_{-600\ to\ -500}$ in our multi-channel comparison ($t^2$; $P = 0.09$), but believe this to be reflective of statistical power as a substantial reduction in amplitude (e.g. 43 – 67%) was observed after training. Post hoc power analysis using our sample size, $\alpha = 0.05$, and our observed effect size $d = 0.80$ yielded an achieved power estimate of $1 - \beta = 0.66$. Thus, although care must be taken in interpreting such results, a non-significant trend towards decreased $BP_{-600\ to\ -500}$ was observed.

In the study of Kita et al. (81), the distributions of potentials between athletes and non-athletes were also compared using topographical maps [c.f. Fig 2; (81)]. These maps indicated that activity was significantly more localized in athletes. The authors speculated that habitual training involving wrist extensions caused initially diffuse brain activation to become specific. Evidence of increased spatial localization of potentials was also observed in the topographical maps of the present study (Fig 4). It is important to note that the absence of the lateralized activity normally associated with upper extremity movements is not surprising given the arrangement of the motor homunculi and is consistent with the findings of other studies examining lower extremity recordings (97, 159). Finally, it is interesting to observe changes after only nine training sessions in contrast to the years of habitual training examined by the Kita et al. study (81).

*Comparison to evoked responses.* Our findings are convergent with prior demonstrations of attenuated cortical activity in response to short-term training. Taube et al. (143) reported a reduction in corticospinal excitability that was correlated with improved motor performance (e.g. postural stability) following four weeks of balance

training. Excitability was assessed using a collision technique of sub-threshold TMS and H-reflex as described elsewhere (109). In brief, this technique is able to attenuate the influence of spinal excitability by adjusting the H-reflex to a specific level, therefore if changes are observed they are most likely reflective of cortical excitability (143). As a result, conditioning of the H-reflex with TMS is considered more reliable than TMS alone to infer changes in cortical excitability (103). Schubert et al. (129) also used the conditioned H-reflex to identify supraspinal changes in response to either four weeks of balance or explosive resistance training of the lower limbs. Both balance and resistance training improved RFD concomitant with a diminished facilitation of the conditioned H-reflex after training. In addition, they also observed no adaptation in reflex gain via the unconditioned reflex, suggesting that changes in the firing rate or intrinsic properties of spinal motor neurons were not responsible for the modulation of the conditioned H-reflex (129). Consequently, observed changes were interpreted mainly as changes in cortical excitability.

Schubert and colleagues' interpretation is in contrast to that of Carroll et al. (21) who suggest that resistance training does not elicit substantial modification of motor cortical centers; rather, it exhibits its greatest influence on the functional properties of the spinal cord circuitry. In that study, subjects performed four weeks of resistance training of the first dorsal interosseous. After training, MVIC increased by 33%, but no change in TMS-induced MEPs was evident at rest or at contraction intensities below 40% MVIC. Only at higher contraction intensities (e.g. 40 – 60%) were MEPs reduced. Similarly, Jensen et al. (79) found no evidence of increased cortical excitability following four weeks of biceps brachii resistance training that increased MVIC by 32%. Unlike Carroll

and colleagues, they observed a significant depression in maximal MEP amplitude at rest, and only a similar trend during tonic contraction. Decreased corticospinal excitability at rest was not correlated to changes with strength, leading the authors to suggest that the observed strength gain was unrelated to cortical changes.

Jensen et al. (79) suggested that slight differences between their findings and that of Carroll et al. (21) may be explained by the variability of recordings during voluntary contractions, supported by the finding that cortical and spinal excitability is better maintained at low intensity stable contractions (33). This variability underscores the role of voluntary effort and lack of consistency amongst studies. For example, Griffin and Caffarelli (64) found no changes in MEP at rest following four weeks of plantar-flexion resistance training, but found a 32% increase in MEP during a 10% MVIC contraction. Although Jensen and colleagues studied the upper extremity, they did not find an increase in MEP during a baseline contraction of 5% MVIC. Presumably, techniques such as the conditioned H-reflex (129, 143) as well as the methods of the present study may circumvent some limitations related to voluntary effort.

*Paradigm considerations*. Direct comparisons of results of the present study to those utilizing evoked responses are difficult for several reasons. Foremost, interpretations of volitional drive and/or cortical excitability are drawn from peripheral EMG assessment whereas the present study records activity at the level of the cortex. Moreover, in order to resolve the MRCP from spontaneous EEG activity, multiple trials are necessary in order to generate a stable average and improve signal to noise ratio. This is in contrast to H-reflex or MEP designs that elicit a response at rest or during tonic contraction. While MRCPs may rely more directly on central nervous system activity,

evoked responses may be more conducive for evaluating the functional state of the corticospinal pathway as they represent excitatory and inhibitory interactions occurring at various levels of the neuraxis (10). Unique features of each technique contribute to the understanding of cortical reactivity and connectivity and its resultant adaptations, as underscored by recent technical advances permitting the combination of TMS-EEG (102). Future studies are warranted to compare changes amongst MRCP characteristics with modifications of cortical and spinal excitability.

We acknowledge that the present investigation lacks a detailed assessment of peripheral adaptation (i.e. EMG sites). Due to practical limitations (e.g. available channels for bipolar recording), we were unable to assess the full musculature involved in the leg extension task. This may be a potential shortcoming by limiting our ability to quantify the relative amount of central and peripheral adaptation that occurs in response to resistance training. Future studies should consider a larger EMG recording montage.

The present study is unique in many aspects. This is the first study to report supraspinal adaptations in response to short-term resistance training using the MRCP paradigm. Moreover, recordings of MRCP associated with lower-extremity movements have been infrequently obtained (159). To our knowledge, an examination of *multi-joint* movements as employed here has not been previously performed. The greater MRCP responses in comparison to reports in the existing literature may, in fact, be the result of performing movements requiring action across several joints. This is in agreement with increased responses observed when movements are more complex (50, 51). The multi-joint training protocol is also unique to the literature investigating neural adaptive effects with short-term resistance training which has primarily studied single-joint actions such

as index finger flexion (21), ulnar deviation (52), elbow- (79), and plantar- flexion (36, 62, 70, 86). We note in passing the importance of these findings in suggesting that the MRCP method may be useful in the study of multi-joint movements relating to key daily activities including gait and the maintenance of posture.

*Conclusion*. In advance of significant muscle architectural and contractile changes in the first few weeks of a program of resistance training, neural adaptive effects are thought to predominantly govern the observed increases in force output (i.e. MVIC). Evidence of adaptation at multiple levels of the neuraxis has been reported previously (1, 56, 58, 63), yet direct evidence of supraspinal adaptation has been lacking. The present data are consistent with the conclusion that adaptations in response to short-term resistance training at the level of the cerebral cortex, reflective of enhanced neural economy. These insights into the mechanisms of neuronal plasticity have implications for disciplines such as neurorehabilitation. The MRCP protocol offers an important approach to the study of early phase neural adaptations during a program of resistance training.

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Association. Additional support was provided by NIH grants T32HD007434 (Program in Physical Therapy) and 1K01HD048437 (G.M. Earhart).

**Figure 3:**

Illustration of experimental setup.

*Note*: Individual adjustments were made to accommodate 80° and 120° of knee and hip flexion, respectively.

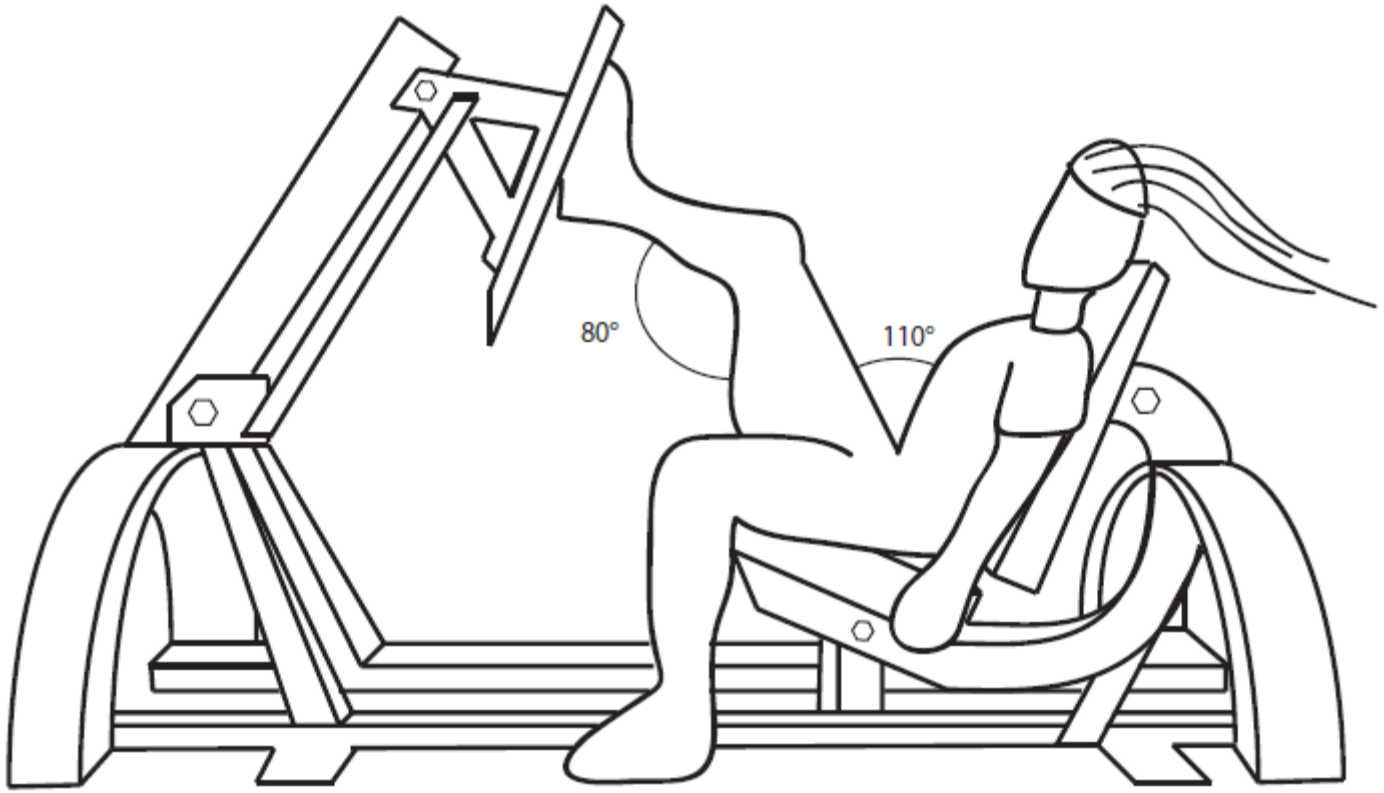

80°
110°

**Figure 4:**

2D topographical maps of component amplitudes

*Note:* Each map is oriented such that the anterior-posterior axis is arranged vertically (i.e. nasion is located at the top).

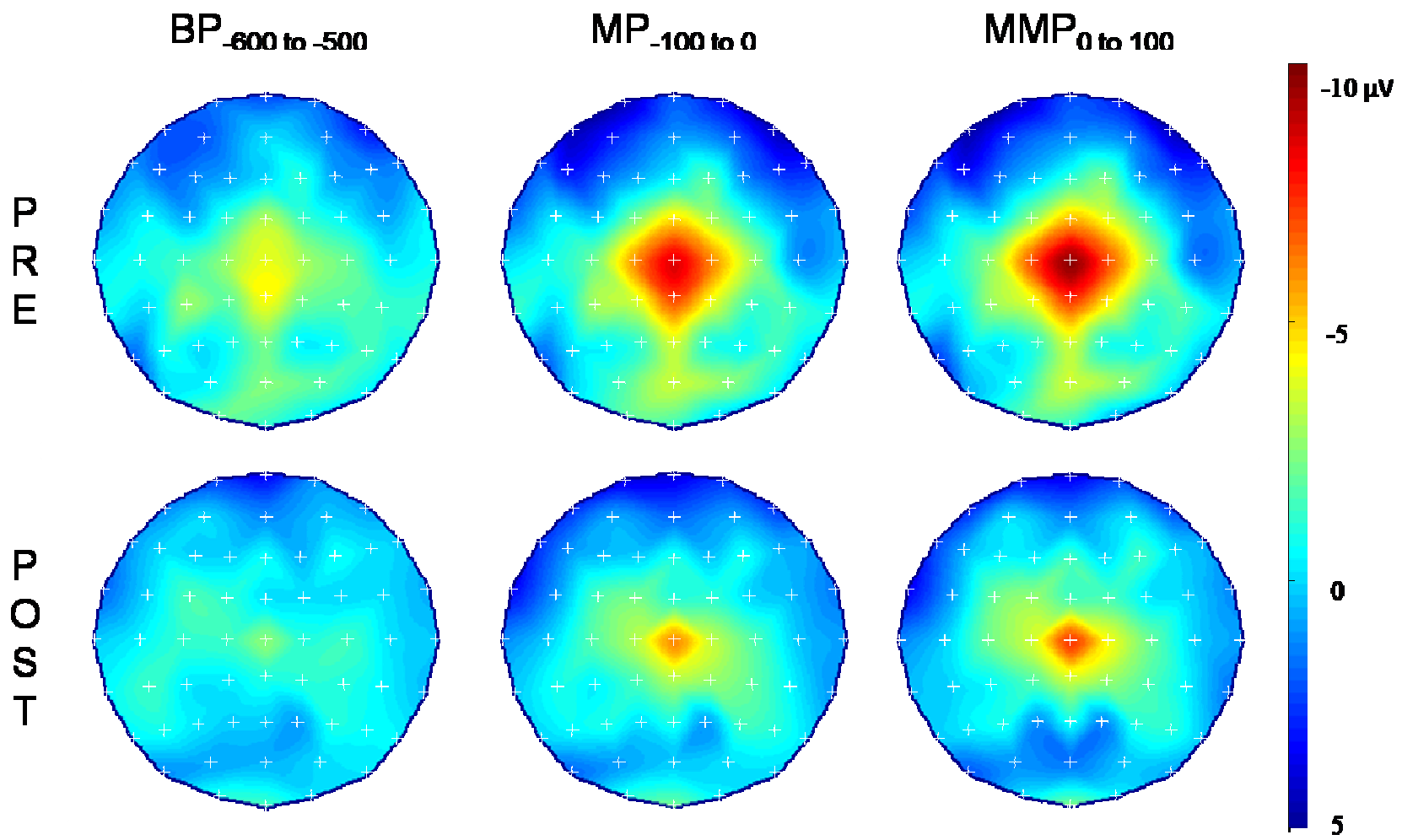
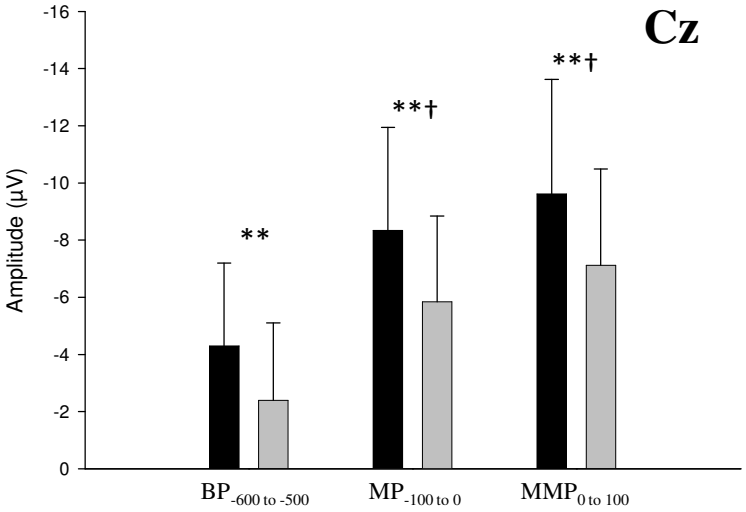
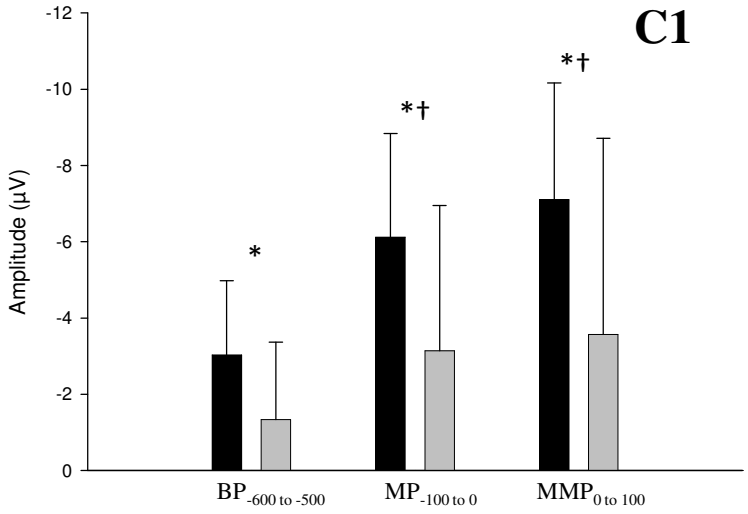

BP-600 to -500
MP-100 to 0
MMP0 to 100
PRE
POST
-10 µV
-5
0
5

**Figure 5:**

MRCP amplitude measures (μV).

*Note:* Amplitudes for each component before (black) and after (gray) training. Error bars are standard deviation. Hotelling $t^2$: †$P < 0.05$; Paired t-test: ** $P < 0.01$, *$P < 0.05$


Cz
Amplitude (μV)
-16
-14
-12
-10
-8
-6
-4
-2
0
**
**†
**†
BP-600 to -500
MP-100 to 0
MMP0 to 100


C1
Amplitude (μV)
-12
-10
-8
-6
-4
-2
0
*
*†
*†
BP-600 to -500
MP-100 to 0
MMP0 to 100

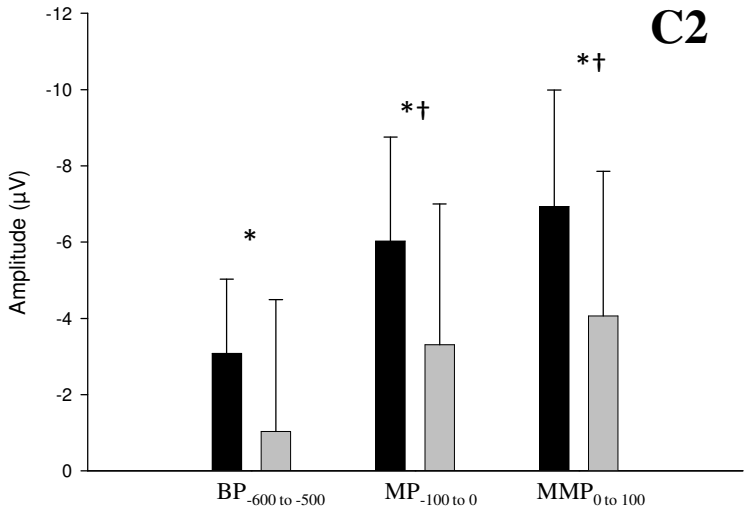
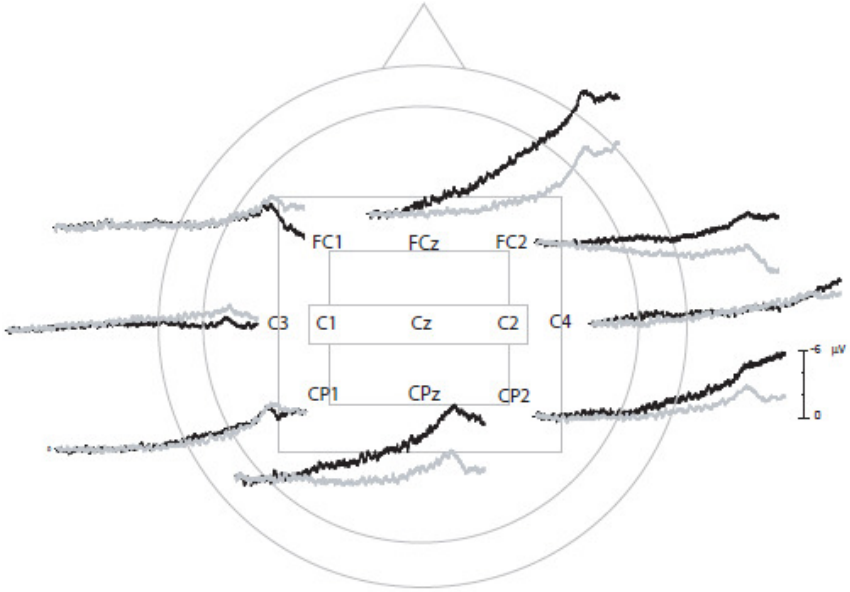
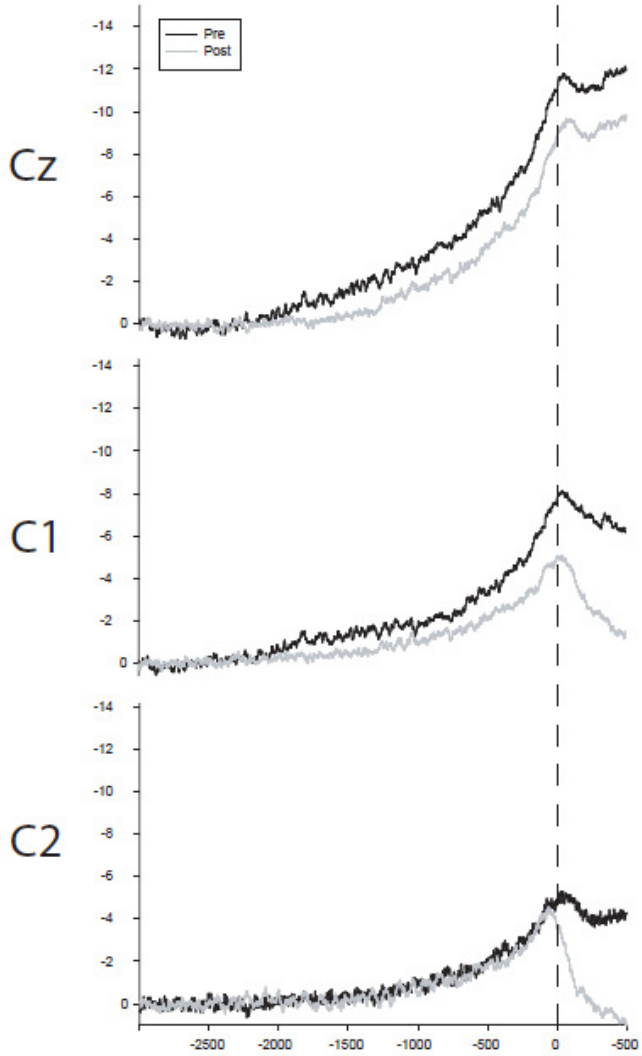

C2
Amplitude (μV)
-12
-10
-8
-6
-4
-2
0
*
*†
*†
BP-600 to -500
MP-100 to 0
MMP0 to 100

**Figure 6:**

Grand average waveforms of MRCP and multi-channel display

*Note:* Grand average waveforms are presented for Cz, C1, and C2 both before (black) and after (gray) training. Dashed line represents the onset of movement. Multiple electrode sites around those of interest (e.g. Cz, C1, C2) are also displayed


FC1
FCz
FC2
C3
C1
Cz
C2
C4
CP1
CPz
CP2
-6 µV
0


Pre
Post
Cz
C1
C2
-14
-12
-10
-8
-6
-4
-2
0
-2500
-2000
-1500
-1000
-500
0
-500

## Chapter 3:

## Central adaptations to repetitive grasping in healthy aging and Parkinson disease.

**Abstract**

***Objective:*** Augmented cortical activity during repetitive grasping mitigates a decrease in cortical efficiency in young adults. It is unclear if similar adaptive processes occur with healthy aging and Parkinson disease (PD).

***Methods:*** Movement-related cortical potentials (MRCP) were recorded during 150 repetitive handgrip contractions at 70% of maximal voluntary contraction (MVC) in three experiments: 1) young versus old, 2) old versus PD 'off' medication, and 3) PD 'off' versus 'on'. MRCP data were grouped into blocks (block 1: trials 1 – 60; block 2: trials 91 -150) and analyzed separately to determine the effects of aging, PD, and PD medication.

***Results:*** We observed no change in EMG or MVC for any group. Significant interactions ($p < 0.05$) were observed at mesial (FCz, Cz, CPz) and motor (C1, C3, Cz) electrode sites for young versus old comparison (experiment 1), with younger adults demonstrating significant increases in MRCP amplitude. No interactions were found for experiments 2 or 3.

***Conclusions:*** Focal activity in cortical motor regions was uniquely augmented in younger adults, but minimal changes were observed in older adults with and without PD.

***Significance:*** Central adaptive processes for the maintenance of task performance changes across the lifespan whereby activation is more localized in younger adults.

## 1. Introduction

Age-related reorganization of the central nervous system is evident during simple motor tasks as characterized by electroencephalography (EEG) (61, 76, 126, 140, 162), functional imaging (fMRI) (107, 155-157), and transcranial magnetic stimulation (TMS) (112, 141, 142). Some consistent findings have been reported regarding task-related activation whereby cortical activity is more diffuse and less lateralized in advancing age (16). Presumably, these findings may be explained in terms of adaptive plasticity in the motor system by which older adults seek to maintain performance despite age-related changes in the brain (156). Such changes include reduction of gray and white matter (60, 95), degradation of cortical neurons (42), connectivity changes in cortical motor regions (123), and a reduction in intra-cortical inhibition (112, 142). Activation of a wider cortical network should not be viewed simply as an effective compensatory mechanism to match performance with a younger counterpart, but also an indication of the inability to selectively activate a given cortical network or region (76).

Subcortical brain structures, e.g. basal ganglia, significantly influence cortical motor regions during movement preparation and execution (29, 54, 113), and are also subject to the effects of aging as well as neurodegeneration. [For review of basal ganglia circuitry: (151)]. Disruption in basal ganglia circuitry, as seen with Parkinson disease (PD), diminishes output to the supplementary motor area (SMA) resulting in hypoactivity. The SMA is involved during movement preparation and functions to initiate movements and integrate them into ongoing motor sequences (30), particularly when those movements are internally guided. Pre-movement hypoactivity has been associated with longer movement durations and slower reaction times in individuals with

PD (31), which is consistent with their clinical profile (i.e. bradykinesia). The effects of PD extend beyond SMA hypoactivity and include dysfunction in several motor cortical areas [See for review: (87)]. Unlike the SMA, primary and premotor cortices demonstrate hyperactivity in PD, with consistent findings across EEG (41), fMRI (67), and TMS (96, 120) studies. Lefaucheur (87) suggests dissimilar changes across motor cortical areas (i.e. hypo- and hyper-activity) may reflect primary or compensatory mechanisms of PD, and underscore the complexity of this disease.

Age-related and neurodegenerative changes in the central nervous system are characterized by task-related central activation patterns, but the majority of these studies focus on simple motor tasks (e.g. button presses, finger-thumb opposition) performed with minimal effort. These limitations may restrict our understanding of plasticity during ongoing motor actions. Such changes may also predispose older adults to a progressive decline in neural drive during repetitive contractions (74), consistent with suboptimal neural output (59). An exercise-related reduction in motor output is typically measured via motor-evoked potentials using TMS (59). Indeed a number of studies have examined cortical excitability during fatiguing contractions (7, 8, 74, 99, 125, 145, 146). Taken together, these studies describe an increase in central motor drive through modulation of excitatory (i.e. increase in corticomotor excitability) and inhibitory (i.e. decrease in intra-cortical inhibition) networks (7). Therefore, adaptations are made in order to compensate for diminished central motor drive and maintain performance of the motor task.

However, changes in excitability may not be analogous with changes in voluntary drive (127). Several studies (57, 80, 93, 127) have investigated central adaptations to repetitive contractions by analyzing movement-related cortical potentials (MRCP), EEG-

derived cortical activity occurring around the time of movement. [For review of MRCP see: (132)]. Contrary to motor-evoked potentials, recording of the EEG does not introduce artificial input into the system and indexes activity at the level of the cortex, and measurements are performed during, rather than following, repetitive contractions (127). Further, as noted by Johnston and colleagues (80), TMS cannot assess global changes occurring simultaneously across the cortex, nor can it discern distinct periods of motor preparation, initiation, and execution. To this end, several EEG studies (57, 80, 93, 127) had subjects perform 120 – 200 repetitive hand grip contractions at a high intensity, and recorded MRCP over the duration of the protocol. Over time, the amplitude of MRCP (i.e. electrocortical activation) significantly increased over SMA and contralateral sensorimotor areas. This increase in MRCP amplitude was interpreted as a central adaptation to counteract suboptimal motor output (127). Thus regardless of methodology (i.e. TMS or EEG) , there appear some consistency amongst findings concerning how the central nervous system may adapt in order to maintain performance during a repetitive or fatiguing task. However, these results are limited primarily to young healthy adults. What is lacking is an understanding of whether this adaptation is present with advancing age, as well as in individuals with central activation impairments (e.g. PD).

We carried out three separate experiments, utilizing the aforementioned MRCP repetitive grasping paradigm (57, 80, 93, 127), to examine the influences of aging and PD on central adaptations. In light of recent work describing age-related EEG differences for baseline motor performance (76), we chose to explore the possibility of an interaction

between age and MRCP amplitude change in experiment 1. We hypothesized the magnitude of adaptation would be attenuated in older adults.

Studies employing self-paced sequential motor tasks, as performed in the present study, have demonstrated reduced activity related to movement preparation for individuals with PD (30, 41, 137). Yet it remains unclear if those with PD retain the relative capability to adapt over the duration of a repetitive motor task similar to those without PD. Therefore, our aim for experiment 2 was to compare those with PD, while off of their antiparkinson medication, to age- and gender-matched controls. Subjects with PD were tested off of their medication in order to obtain a more accurate assessment of the true pathological condition. We hypothesized that their ability to adapt over the duration of the protocol would be compromised in comparison to older adults without PD.

Levodopa has been shown to enhance EEG activity during movement preparation (41) and reverse abnormal cortico-motorneuron activity (96). Consequently, experiment 3 examined the effects of medication by comparing the same individuals with PD on and off of their antiparkinson medication. We hypothesized greater adaptation would be observed in subjects in an optimally medicated state.

## 2. Methods

### *2.1. Subjects*

Thirty subjects volunteered to participate in experiments 1 – 3. Subjects were subdivided into 'young' (age mean ± SD, 24.1 ± 1.0; age range: 22 – 25), 'old' (68.8 ± 4.6; 59 – 78), and PD (68.1 ± 8.4; 59 – 78) groups. Each group consisted of 10 subjects

(8 men and 2 women). Old and PD groups were also age-matched. Subjects with PD (18) were recruited from the Washington University Movement Disorders clinic and their clinical profiles are shown in Table 1.

All subjects were right-handed according to the Edinburgh handedness inventory (110). None had history of musculoskeletal injury or neurological events (other than PD), nor were any depressed or taking any psychoactive medication for at least 6 months prior to entry into the study. All subjects gave their written informed consent to the experimental procedures, which conformed to the Declaration of Helsinki and was approved by the Washington University School of Medicine Human Research Protection Office.

The paradigm for all three experiments was methodologically equivalent, but with unique research questions. Experiments 1 – 3 addressed the effects of aging, PD, and antiparkinson medication, respectively. All subjects performed a single-session protocol, with the exception of individuals with PD. Those with PD performed the protocol after an overnight withdrawal (OFF) of their antiparkinson medication and in an optimally medicated state (ON), i.e. 1 – 2 hours after morning dose. Relative ON and OFF testing sessions were randomized, performed at the same time of day, and separated by a minimum of 72 hours of rest. Data from the old group were analyzed in both experiments 1 and 2, and data from the PD OFF group were analyzed in both experiments 2 and 3.

*2.2. Experimental procedures*

Subjects were comfortably seated in an armchair with their dominant hand and forearm stabilized in a semi-supinated position by a vacuum positioning pillow (See Figure 7). A strain gauge grip dynamometer (Biopac SS25; Goleta, CA) was placed in their dominant hand from which isometric handgrip force was recorded. This dynamometer did not allow for individual adjustments, but subjects were given instruction and practice on how to squeeze the device using a power grip configuration. Thereafter, a maximum voluntary contraction (MVC) was recorded as the largest force produced in a 3 – 5 second attempt. Subjects were given three attempts and the average was used for subsequent analysis. Standardized instructions were provided to all subjects.

Each subject then performed 150 intermittent handgrip contractions at 70% of their MVC, segmented into five consecutive sets of 30 trials. This repetitive grasping was self-initiated and subjects were instructed to contract once every 5 – 8 seconds. In order to maintain the appropriate contraction intensity, real-time visual force feedback was provided by means of a custom LabVIEW program (v8.0, National Instruments). A computer screen positioned at eye-level approximately 0.5 m in front of the subject displayed a large sphere that would illuminate once the subject reached the target force of 70% MVC. Once reached, subjects were instructed to relax immediately (127). MVC was re-assessed following the completion of the fifth set of 30 trials. These procedures were consistent across experiments 1 – 3.

*2.3. Electrophysiological recording*

Continuous EEG was recorded using an appropriately sized 61-channel elastic nylon Quick-cap, and data were acquired using the 70-channel Synamps2 amplifier system using the Scan 4.3 software (Compumedics; Charlotte, NC). Vertical and horizontal electrooculograms (EOG) were recorded using Ag/AgCl electrodes placed above and below the right eye and the left and right outer canthi, respectively. Surface EMG was measured bipolarly using two Ag/AgCl electrodes placed 20 mm apart over the flexor digitorum superficialis (FDS) muscle belly of the dominant arm as identified through palpation. Prior to EOG and EMG electrode application, the skin was cleaned and vigorously abraded. EEG, EOG, EMG, and force from the grip dynamometer were all continuously and synchronously recorded through the Synamps2 amplifier and Scan 4.3 software. This system has a common mode rejection ration of 100 dB, 24-bit A/D resolution, and input impedance of 10 MΩ. Data were recorded with a bandwidth of DC-100Hz and sampled at 1KHz. Impedances were kept below 5 kΩ for all electrodes.

*2.4. EEG analysis*

Offline analysis was performed utilizing custom MATLAB programs (v7.3.0; Math Works, Inc.; Natick, MA). Raw EEG data were inspected visually to identify and remove signal artifacts. Data were high-pass filtered at 0.01 Hz (90 db) to eliminate the baseline shift associated with DC recording and were referred to a common average. For each trial (i.e. repetition), the onset of force was used to synchronize a 4 s epoch, 3 s before the onset and 1 s after. Force onset was defined as the point when the signal from the grip dynamometer exceeded a threshold of two standard deviations above the activity level at the beginning of the epoch and subsequently remained above that level for at

least 500 ms. Non-contaminated epochs were averaged together forming an average MRCP for each participant. This averaging was performed separately on trials 1 – 60 (block 1) and 91 – 150 (block 2), and therefore allowed us to analyze main effects associated with block.

MRCPs were decomposed into three distinct components that have been described and analyzed previously (22, 45, 83, 138, 163): 1) mean amplitude between -600 and -500 ms prior to movement onset, or *Bereitschaftspotential* (BP), 2) mean amplitude between -100 ms and movement onset, or *motor potential* (MP), and 3) mean amplitude from onset to +100 ms, or *movement-monitoring potential* (MMP). These measurement windows were used to characterize the time course of the MRCP. Amplitudes were computed with reference to a baseline of -3000 to -2500 ms prior to movement onset. Onset of negativity (i.e. MRCP onset) was identified as the point when the baseline signal deviated from a 95% confidence interval and subsequently remained above that level for at least 500 ms from the period of -2500 to -2000 ms preceding movement. Our electrode sites of interest were consistent with prior MRCP studies utilizing this paradigm (57, 80, 93, 127) and included: Cz, FCz, CPz, C1, and C3. These electrodes were then grouped into two regions of interest, e.g. left motor region (LM = Cz, C1, C3), and the central mesial region (CM = FCz, Cz, CPz).

Two-dimensional (2D) topographical maps were created to reflect spatial features of the MRCP considering the entire 61-electrode montage. Separate 2D maps were created for each of the three distinct MRCP components for each block, using group mean data. Group mean data rather than single-subject data were used to better represent true cortical activity preceding movement (50).

*2.5. EMG and force analysis*

EMG recorded during repetitive grasping and MVC attempts were band pass filtered in the 1 – 100Hz frequency range and rectified, and maximum amplitudes were calculated. For repetitive grasping, maximum EMG amplitudes were calculated over a 2500 ms epoch (e.g. 1000 ms prior to onset to 1500 ms after onset), and then averaged across trials similar to the MRCP described above. For MVC attempts, maximum amplitudes were computed over the duration of the MVC attempt.

The force signal from the dynamometer was digitally high-pass filtered using a $4^{th}$ order, zero-lag Butterworth filter (5 Hz). Force-time histories were analyzed for peak and mean force during grasping and MVC attempts, respectively. Peak rate of force development (RFD) was also computed as the highest values of the slope coefficients of the tangent computed during a sliding 5 ms window (154).

*2.6. Clinical and subjective rating scales*

Subjects completed the fatigue severity scale (84) or Parkinson fatigue scale (15) depending on assignment to either experiment 1 or 2, respectively. They were also asked to subjectively rate their perceived exertion, RPE (12), at rest and following completion of the repetitive contractions.

The motor subsection of the Unified Parkinson Disease Rating Scale (UPDRS) was administered by the same blinded Movement Disorders Specialist to all individuals with PD, both ON and OFF their medication. This clinician/investigator also rated the clinical disability of those with PD according to the Hoehn & Yahr (HY) scale. Subjects

were also asked to subjectively rate how well they felt their Parkinson symptoms were controlled on a 10-cm visual analog scale prior to testing both ON and OFF conditions. A score of '0' indicated they felt no control over their symptoms whereas a score of '10' indicated they felt complete control over their symptoms. This scale was used to confirm the OFF condition.

### *2.7. Statistics*

MRCP, EMG, and force data were analyzed using a mixed ANOVA design with group and block (block 1, block 2) as between- and within-subject factors, respectively. To account for multiple repeated-measures analyses, $p$ values were based on the Huynh-Feldt corrected degrees of freedom. Post-hoc analyses, with correction, were performed with independent or paired $t$-tests where appropriate. All data are presented as mean ± SD and were analyzed using SPSS (v17; SPSS Inc., Chicago, IL). For all comparisons, a probability of less than or equal to 0.05% was considered to be statistically significant.

## 3. Results

### *3.1. Experiment 1*

Young and old subjects scored similarly and low on the fatigue severity scale (average score = 2.1). Their RPE following completion of the protocol was also similar ($p = 0.751$; Figure 8) and all were able to successfully complete all 150 contractions. Independent two-tailed $t$-test found no difference ($p = 0.198$) at baseline for average MVC for young (51.3 ± 21.9 kg) and old (39.8 ± 16.5 kg) groups, therefore repetitive grasping was performed at similar absolute and relative intensities (Table 2). Two-way

ANOVA found no significant interaction or block main effect for any force or EMG variable during MVC testing. Similarly, no differences were found in force or EMG variables during the repetitive grasping. In addition, the absence of behavioral change between blocks suggests subjects performed the task similarly across blocks. This is supported by similar ($p > 0.05$) inter-trial intervals during blocks 1 and 2 for young (block 1 = 8.6 ± 2.3 s; block 2 = 8.5 ± 2.2 s) and old (5.9 ± 1.6 s; 6.4 ± 1.9) groups. Inter-trial intervals are defined as the time period from force offset of one contraction to force onset of the ensuing contraction (i.e. inter-trial pacing).

Using a mixed ANOVA we observed significant interactions ($F_{(1,18)} = 7.23 – 8.63$, $p = 0.009 – 0.015$) and block main effects ($F_{(1,18)} = 7.62 – 9.89$, $p = 0.006 – 0.013$) for each MRCP component in the CM region. Similarly for LM, we found significant interactions ($F_{(1,18)} = 4.55 – 5.17$, $p = 0.033 – 0.044$) and block main effects ($F_{(1,18)} = 4.67 – 5.33$, $p = 0.035 – 0.047$) for each component with the exception of BP which demonstrated an interaction ($F_{(1,18)} = 4.67$, $p = 0.044$), but no block main effect ($F_{(1,18)} = 2.44$, $p = 0.135$). Paired one-way *t*-tests with Bonferonni correction ($\alpha/6 = 0.008$), indicated significant increases in amplitude from block 1 to block 2 in young subjects for CM (BP, $p = 0.005$; MP, $p = 0.004$; and MMP, $p = 0.005$) and LM (BP, $p = 0.002$; MP, $p = 0.001$; and MMP, $p = 0.001$) electrode clusters. Paired *t*-tests failed to demonstrate significant block differences in the old group. Onset times demonstrated a main effect for block for CM ($F_{(1,18)} = 9.07$, $p = 0.008$) and LM ($F_{(1,18)} = 4.17$, $p = 0.054$), but only LM showed a significant interaction ($F_{(1,18)} = 5.30$, $p = 0.033$). Paired one-way *t*-tests ($\alpha/2 = 0.025$) found onsets began earlier for young subjects at CM ($p = 0.006$) and LM ($p = 0.008$), but only at CM ($p = 0.036$) for the old group. Mean data are presented in

Figure 9A. Waveforms in Figure 10 are representative of group mean data for CM and LM electrode clusters. 2D spatial plots (Figure 11) are also comprised of group mean data, and activity was plotted for time intervals defining the three MRCP components.

*3.2. Experiment 2*

Subjects with PD reported to the laboratory after an overnight withdrawal of their medication (12.85 ± 2.7 hours). Medication withdrawal was confirmed with significantly ($p = 0.05$) higher UPDRS motor scores (Average score; OFF = 28.3, ON = 25.3) as well as lower values on the 10 cm visual analog scale ($p = 0.04$; OFF = 6.5, ON = 8.5), analyzed using one-tailed *t*-tests. Two of the subjects with PD were unable to complete their fifth block of 30 contractions; therefore, their data, along with their matched controls' data were subsequently analyzed comparing trials 1 - 60 (block 1) and 61 – 90 (block 2). [Note that paired *t*-tests found no difference in amplitude for any component during block 2 whether computed from trials 61 – 90 or 91 – 150 in our two older adult control groups. Therefore, figures were prepared using data from trials 91 – 150 to maintain consistency with experiment 1.]

Individuals with PD had higher scores on the Parkinson Fatigue scale than older controls (PD: 2.3 ± 0.9, Old: 1.38 ± 0.4; $p = 0.007$), but this sample was not considered fatigued (15). RPE following the protocol were higher ($p = 0.008$) in individuals with PD (Figure 8). EMG and force variables from MVC attempts and repetitive grasping failed to show any significant differences using two-way ANOVA ($p > 0.05$). Average MVC was similar ($p = 0.35$) between old (39.7 ± 16.4 kg) and PD OFF (32.4 ± 17.9 kg) groups at baseline, indicating task performance was performed at similar absolute and

relative intensities (Table 2). In addition, inter-trial intervals were also similar across blocks for each group. Two-way ANOVA failed to demonstrate any interaction or block main effects for any MRCP component or onset time at either electrode cluster ($p > 0.05$). MRCP amplitude data are shown in Figure 9B. Group waveforms and 2D plots are illustrated in figures 12 and 11, respectively.

*3.3. Experiment 3*

Baseline MVC was similar ($p = 0.456$) for subjects irrespective of medication (ON, 35.3 ± 18.6 kg; OFF, 32.4 ± 17.9 kg; Table 2), thereby repetitive grasping intensities were also similar. A paired one-tailed *t*-test indicated higher RPE following the protocol when subjects were OFF ($p = 0.033$; Figure 8). Two-way ANOVA found no significant ($p > 0.05$) interaction or block effects for any EMG or force variable during MVC attempts or grasping. Further, inter-trial intervals also demonstrated similar performances between blocks ($p > 0.05$).

No significant group-by-block interactions were observed for any MRCP component or onset time at either CM or LM clusters ($p > 0.05$). A block main effect was observed only at MP ($F_{(1,18)} = 7.34$, $p = 0.014$) and MMP ($F_{(1,18)} = 7.89$, $p = 0.012$), but only for CM cluster. One-tailed paired *t*-tests, with correction ($\alpha/3 = 0.02$), found significant amplitude increases at CM from block 1 to block 2 at BP ($p = 0.038$), MP ($p = 0.013$), and MMP ($p = 0.005$). These increases were only observed in PD ON, and PD OFF demonstrated no significant change in amplitude from block 1 to block 2 ($p > 0.05$). Mean MRCP amplitude data are shown in Figure 9C. Group waveforms and 2D plots are illustrated in figures 13 and 11, respectively.

## 4. Discussion

In the present study, electrocortical activation was investigated during repetitive grasping to understand age, pathology, and medication influences on central adaptation. Therefore, the ensuing discussion will separately address each research question.

### *4.1. Effect of aging (Experiment 1)*

Similar to prior MRCP studies in healthy young adults (57, 80, 93, 127), we observed a significant increase in activity over both central mesial and contralateral motor areas over time (Figure 10). However, this adaptation was absent or minimal in older adults, indicating an age-related difference in central adaptation during repetitive grasping in agreement with our hypothesis.

As mentioned in the introduction, task-related activation studies demonstrate less focused and more diffuse activity in older adults (16, 155) concomitant with over-activation of mesial and sensorimotor areas (76, 107, 126, 140, 156). These observations are derived from simple motor tasks (e.g. button presses, finger-thumb oppositions, joystick movements) that are less physically demanding than the cumulative effects of the repetitive grasping paradigm employed herein. Though, if we consider only block 1 of the present study as representative of a more 'simple' motor task, we also observe more focused and lateralized activity (Figure 11) in agreement with previous studies. Further, we found that older adults exhibit greater activation over CM and LM regions (Figure 10) when examining only block 1. However, the purpose of our study was not to confirm well-established findings, but rather to extend these findings to better understand central adaptive processes during repetitive grasping paradigm. To our knowledge, no studies

have examined age-related differences in brain activation patterns during such a paradigm, but several are available in healthy young adults (6-8, 57, 80, 92-94, 99, 127). From this, young adults demonstrate an increase in central motor drive (e.g. premotor, motor, sensorimotor) to counteract suboptimal voluntary drive. Our results in young adults confirm these findings in that cortical activity increased progressively for each MRCP component (BP, MP, MMP) over CM electrodes and for most components (MP, MMP) over LM electrode sites. In addition, MRCP onset began earlier over sensorimotor regions, further reflecting supraspinal adaptation responsible for movement preparation and execution. However, similar findings were not obtained in older adults where adaptation was attenuated, i.e. no differences observed between blocks 1 and 2.

In addition to adaptation within cortical motor centers, another possible countermeasure would be the involvement of additional brain regions to maintain sufficient neural drive, which has been interpreted as a increase in central effort (46). In a previous study, fMRI data recorded during intermittent handgrip contractions demonstrated a progressive increase in activity in ipsilateral sensorimotor cortex, prefrontal cortex, cingulate gyrus, and cerebellum (92). The investigators reasoned that similar to motor neuron pools in the spinal cord, the brain may also recruit more cells into action (92). Enhanced brain activation may also be a function of the increase in sensory feedback during repetitive grasping (94). Alternatively, Liu and colleagues have proposed the "shifting of activation center" hypothesis to explain the recruitment of additional brain regions (91). They hypothesize that the brain has multiple motor control centers with parallel projections to motor neuron pools; therefore, if neurons in one location become unable to maintain adequate output, the brain may shift activation to

another group of neurons. Through EEG source reconstruction, these authors demonstrated that during 200 unilateral maximal handgrip contractions, the center of brain activation shifted in the direction of anterior, inferior, and ipsilateral locations (91). This concept has recently been supported via EEG-EMG coherence maps recorded during sustained fatiguing elbow flexion which demonstrated augmented ipsilateral activation (161). As simplified by Yang et al., under normal circumstances, contralateral M1 controls voluntary muscle contractions directly via monosynaptic corticospinal pathways which is underscored by strong beta (15 – 30 Hz) band coherence. Presumably, as the brain shifts to more indirect polysynaptic pathways to muscle, i.e. shifting the activation center, a weakened coupling would be expected (161).

There appears to be converging and consistent evidence of central adaptive processes during repetitive grasping, but adaptation appears significantly blunted in CM and LM regions of interest for older adults. Several possible mechanisms may explain these findings. In response to age-related deterioration of the nervous system (e.g. shrinkage of M1, loss of neurons), older adults recruit larger neuronal populations (76, 155) to produce an intended movement. Greater activation may also be the result of the normal aging process in which integration of sensorimotor processing becomes less efficient. In other words, greater computational effort is required on the part of older adults to perform a task at the same level as a younger adult and this effort is reflected at the systems level (156). This would seem plausible as information processing related to anticipation and preparation of a motor response changes with age. These changes are related to alterations in cognitive processes that engage pre- and supplementary motor areas, areas subject to structural changes with aging (140).

Studies have also observed the absence of lateralized activity (140) or a shift towards ipsilateral M1 activation with increasing age (107, 141, 157), likely due to reduction in interhemispheric inhibition (112, 142). Ipsilateral deactivation of M1 is believed to occur through transcallosal inhibition, which may be impaired or reduced in older subjects (156, 157). Along with activation of a wider cortical network, this shift in activation may also be in agreement with Liu and colleagues' shifting of activation center hypothesis. All of these studies fit into a similar physiological concept, namely that the aging brain would need to mobilize additional primary and non-primary motor resources to accomplish successful task performance (126). We speculate that given the finite resources available in central sensorimotor and premotor regions, older adults may need to recruit additional networks that subserve motor function.

*4.2. Effect of Parkinson disease (Experiment 2)*

Contrary to our hypothesis, we observed no between-group difference in MRCPs, a function of minimal (non-significant) changes across blocks 1 and 2 for both groups. Clearly, individuals with PD have central activation impairments given the noted lower MRCP amplitudes (Figure 12) in agreement with previous studies (30, 41, 137), but with regard to central adaptation there appears little difference between those with and without PD.

Age-related changes discussed above (*Section 4.1*) are also applicable to individuals with PD as our samples were matched for age. There are also several unique aspects of PD that may affect the potential for central adaptation, most notably the result of disrupted basal ganglia circuitry. Abnormal drive along the basal ganglia-

thalamocortical motor circuit impedes facilitation of desired movement and presents with cortical abnormalities. Cortical excitability changes during movement preparation and execution demonstrate failure of volitional activation (49), supportive of clinical manifestations of bradykinesia and akinesia. It has been suggested that intracortical or thalamocortical facilitatory inputs may fail to fully activate the cortical areas necessary for an intended movement (87). This failure may be represented by the hypoactivity clearly demonstrated in Figures 11 – 12.

Although the present study quantifies adaptation in terms of changes in MRCP amplitude, the spatial extent of activation (e.g. spatial depth) may reveal important changes that are unable to be captured by the present experiment. A recent study has demonstrated that individuals with PD utilize active motive reserve, whereby novel motor areas are activated to compensate for normal motor networks that are limited (111). In this study, subjects were asked to perform a sinusoidal handgrip force task at different frequencies (0.25, 0.5, and 0.75 Hz) while OFF of their antiparkinson medication. In healthy controls, activity of widespread motor networks increased monotonically with movement speed whereas those with PD recruited this 'normal network' to a greater extent even at the lowest frequency. Palmer and colleagues suggest that although those with PD retain the ability to recruit the normal network, they do so to a greater extent albeit with greater physiological cost (111). Further, a different PD-specific network emerged that included more involvement of the cerebellum concomitant with reduced activation of the thalamus and basal ganglia. Therefore activation of their motor reserve (i.e. increased effort) in order to maintain normal behavioral output is secondary to a

maximally recruited normal network and may likely include greater or lesser involvement of structures comprising the normal network.

Although speculative, it is interesting to consider these findings in the framework of the present study. Presumably, if the window for augmented activation is narrow in PD, very little adaptation over our protocol would be expected in our electrode regions of interest (i.e. normal network). In other words, these regions of interest may be maximally activated during the initial phase of the repetitive grasping paradigm and those with PD must utilize their motor reserve (e.g. subcortical structures) to retain an optimal level of task performance. This interpretation is consistent with age-related compensation (91, 126) as well as our findings, but confirmation requires more sophisticated techniques than the present study. Future investigations are needed to further resolve the mechanisms responsible for these central adaptive processes.

*4.3. Effect of antiparkinson medication (Experiment 3)*

In simple motor tasks, antiparkinson treatment has been shown to increase BP amplitude in individuals with PD (40) and normalize cortical excitability (96). In the present study, we did not find any significant interactions for any variables suggesting medication did not significantly affect central adaptive processes herein. However, we did observe a main effect for block at MP and MMP over CM regions. This block main effect appears driven by changes observed in PD ON rather than PD OFF (Figures 9 and 13). In other words, what minimal adaptation we observed in PD OFF was enhanced during PD ON. Specifically, amplitudes for each component were approximately 30% higher during block 2 for PD ON as compared to PD OFF.

Medication resulted in an approximately 10% improvement in UPDRS motor score which although small, exceeded the minimally clinically important change (128, 134). Dopaminergic drugs may exhibit influence over inhibitory parameters as assessed by TMS (104, 115) and these pathways are most affected in PD (19, 87). By restoring inhibitory control, motor disturbances may be attenuated by selecting more appropriate motor programs. As a result, various studies have shown dopaminergic treatment to reduce M1 hyperactivity and reverse hypoactivity in SMA (87). Presumably, these effects may account for the significant increases in amplitude at BP, MP, and MMP over CM electrode sites.

Alternatively, enhanced activation in these regions may also reflect focusing effects of levodopa (108, 111). From the Palmer et al. study discussed in *Section 4.2*, individuals with PD were also tested ON their medication and authors reported that those with PD did not activate their motor reserve to the same extent as when OFF medication. This was achieved by a reduction in the spatial variance of activation within regions of interest in a manner that normalized motor activity (108, 111). Ng and colleagues (108) suggest that levodopa may exhibit system-level effects by refocusing the activation of cortical and subcortical structures. Even though the methods and paradigm of the present study do not allow a direct comparison, it appears plausible that focusing effects of levodopa may account for our observed increases in CM electrode sites. It should be noted that such an effect may not be specific to PD, as levodopa has also been shown to influence premotor processing when administered to neurologically normal adults (40, 66).

*4.4. Study considerations*

A detailed assessment of multiple EMG sites is lacking in the present investigation as a result of practical limitations with our recording system, i.e. limited available channels for bipolar recording. Therefore, it may be questioned whether cortical changes are manifested by recruitment of non-prime movers of the involved arm as well as activation of contralateral musculature (i.e. mirror movements). We do not consider these significant problems for two reasons. First, all subjects were provided a thorough familiarization that specifically focused on activating the involved hand for gripping and were continuously monitored. Also, if unwanted movements were made during performance of a trial this would likely interject movement artifacts within the EEG recording which is screened for and eliminated during data analysis. Second, larger EMG montages including assessment of contralateral musculature (e.g. finger, arm, shoulder sites) has been performed in three separate studies employing 100 – 200 intermittent handgrip MVCs (91, 93, 94). EMG activity of the prime and non-prime movers of the contralateral limb remained low and similar to pre-exercise values, and activity of the non-prime movers of the involved limb did not significantly change over the protocol and remained low (91, 93, 94). As the present study utilized the same intermittent handgrip design, albeit at a 30% lower intensity, we expect minimal contribution from muscles outside of the prime movers of the involved hand.

Despite substantial increases in RPE from baseline (young: + 47%; old: +45%; PD OFF: +96%; PD ON: +68%), we observed no significant changes in MVC or EMG. This differs from a previous study in young adults where following 120 handgrip contractions at 70% MVC, post-exercise MVC was 58% of its baseline value (80).

However, subjects of this study were asked to maintain 70% MVC contraction level for four seconds after reaching the target whereas in our study subjects immediately relaxed after reaching the target. Despite this, our observed increases in MRCP are consistent with and support previous findings (80), albeit their MRCP amplitudes on average were higher particularly during the MP phase of the MRCP waveform. Our protocol more closely replicates that performed by Schillings and colleagues (127) in which subjects were also instructed to relax after reaching the target 70% MVC. Although their protocol included 50 more contractions than the present study, they also were unable to demonstrate a significant decrease in MVC or increase in EMG. The authors suggested their observed increase in MRCP amplitude reflects diminished efficiency of the motor cortex.

*4.5. Conclusions and future directions*

Successful performance of repetitive grasping reflects the adaptable and plastic nature of cortical networks governing motor function. Age-related and neurodegenerative changes that occur during normal aging and with pathology underscore this plasticity. From our data, it appears that cortical regions relied upon for dominant hand grasping (premotor, contralateral motor) may sufficiently augment activity to maintain an appropriate level of motor output. For this protocol, however, it appears this central adaptation is attenuated with aging. As a result, older adults may rely upon mobilization of additional brain regions, in support of a shifting of activation hypothesis (91). This adaptation is likely due in part to a greater central effort at baseline. For individuals with PD who have known central activation impairments, they

may rely upon unique activation strategies in comparison to healthy older adults to successfully complete a motor task (111). Further, administration of antiparkinson medication (PD ON) results in only minimal changes in comparison to PD OFF. Future research is needed to clarify these mechanisms in individuals with and without PD, considering amplitude as well as spatial-depth changes, as amplitude alone may not be sensitive in discriminating effects (108, 111).

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**Figure 7:**

Illustration of experimental protocol.

*Note*: Subjects were seated in a semi-recumbent position and computer monitor was placed at eye-level at a distance of approximately 0.5 m.

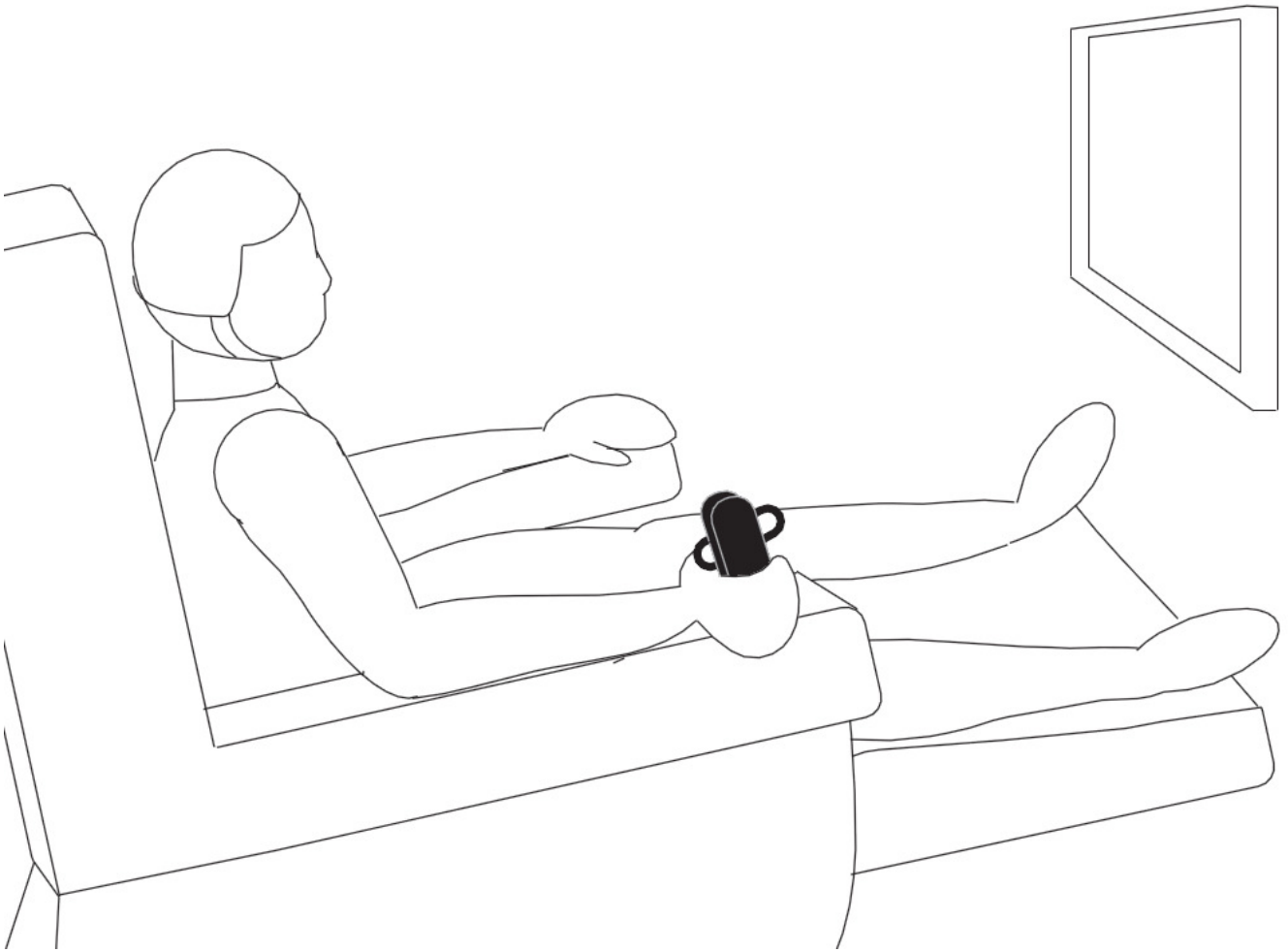

**Figure 8:**

Ratings of perceived exertion (RPE) recorded at baseline (Pre) and immediately following their final set of 30 trials (Post). The RPE scale (12) ranges from a score of 6 (very light) to 20 (maximum effort). Error bars are in standard error units.

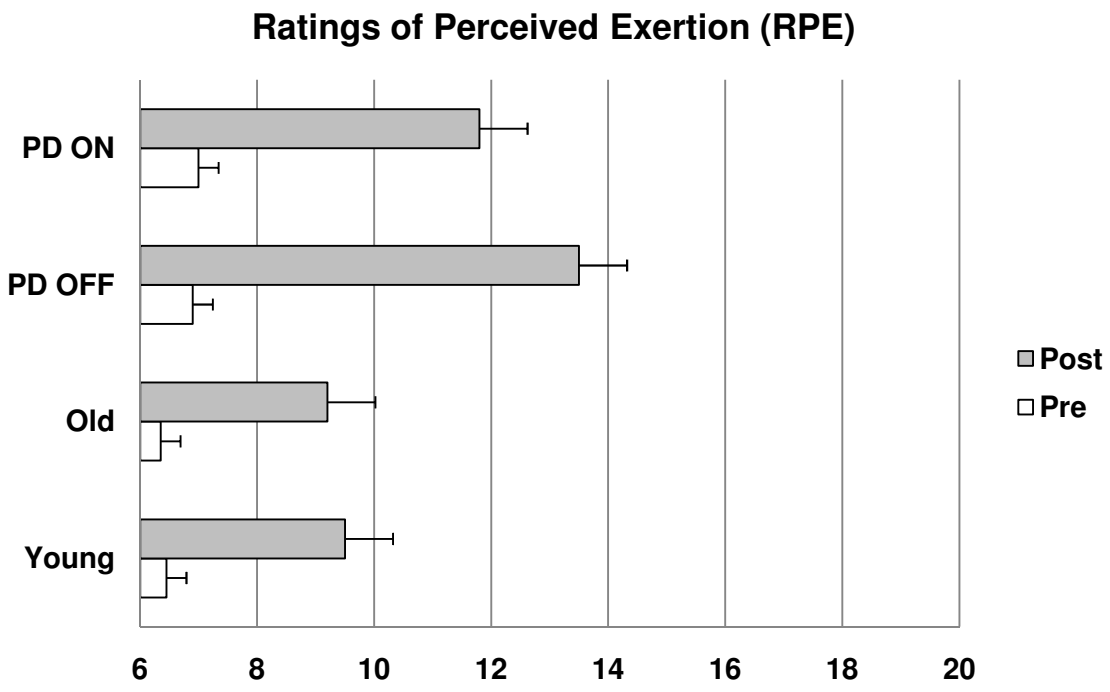
Ratings of Perceived Exertion (RPE)
PD ON
PD OFF
Old
Young
6
8
10
12
14
16
18
20
Post
Pre

**Figure 9:**

Grand averaged BP, MP, and MMP amplitude for central mesial (CM) and left motor (LM) electrode sites across the top and bottom panels, respectively. Results from experiments 1 (A), 2 (B), and 3 (C) are shown from left to right. Error bars are in standard error units.

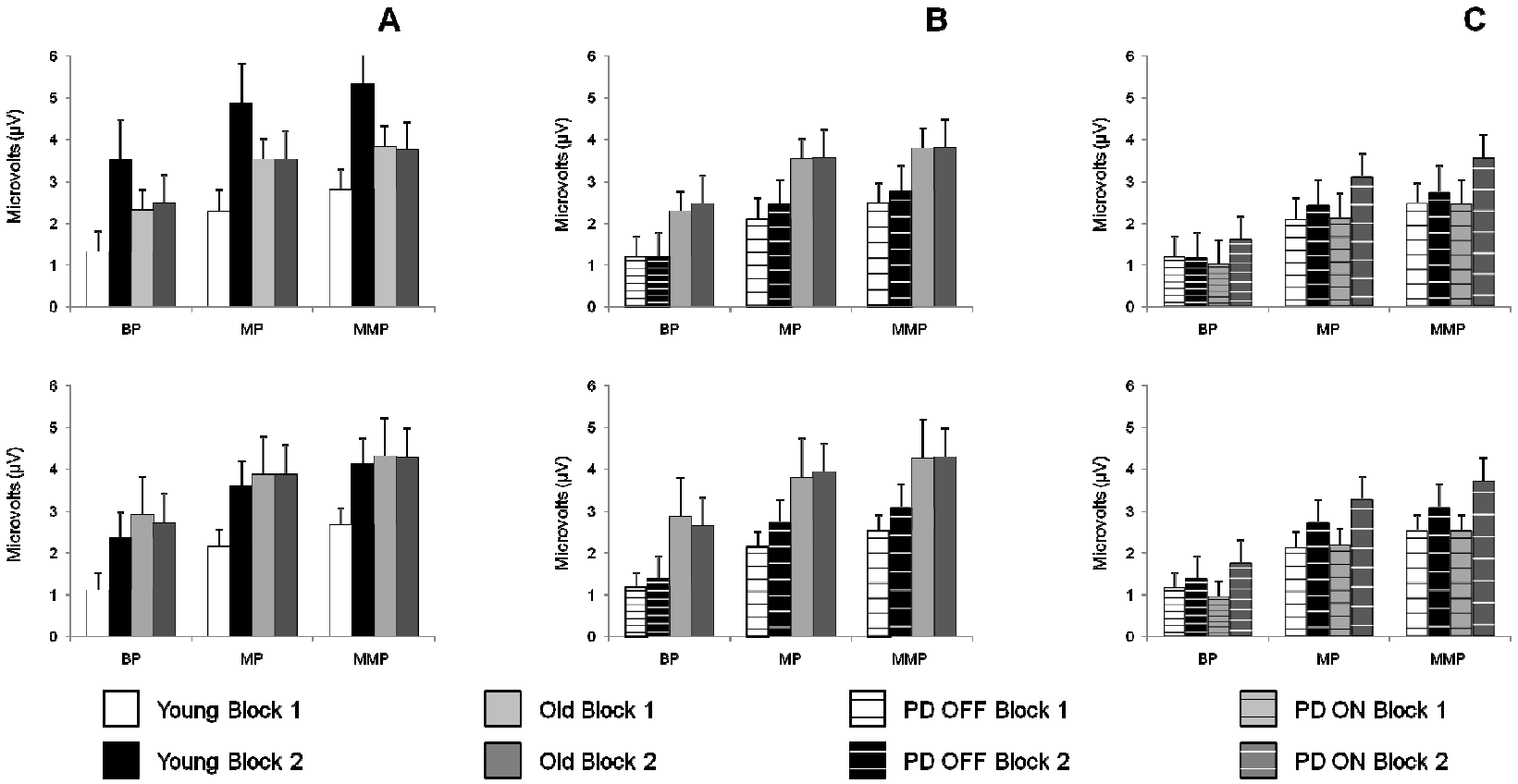
A
B
C
Microvolts (μV)
0
1
2
3
4
5
6
BP
MP
MMP
Young Block 1
Young Block 2
Old Block 1
Old Block 2
PD OFF Block 1
PD OFF Block 2
PD ON Block 1
PD ON Block 2

**Figure 10:**

Grand average MRCP waveform at CM (top) and LM (bottom) electrode sites for experiment 1.

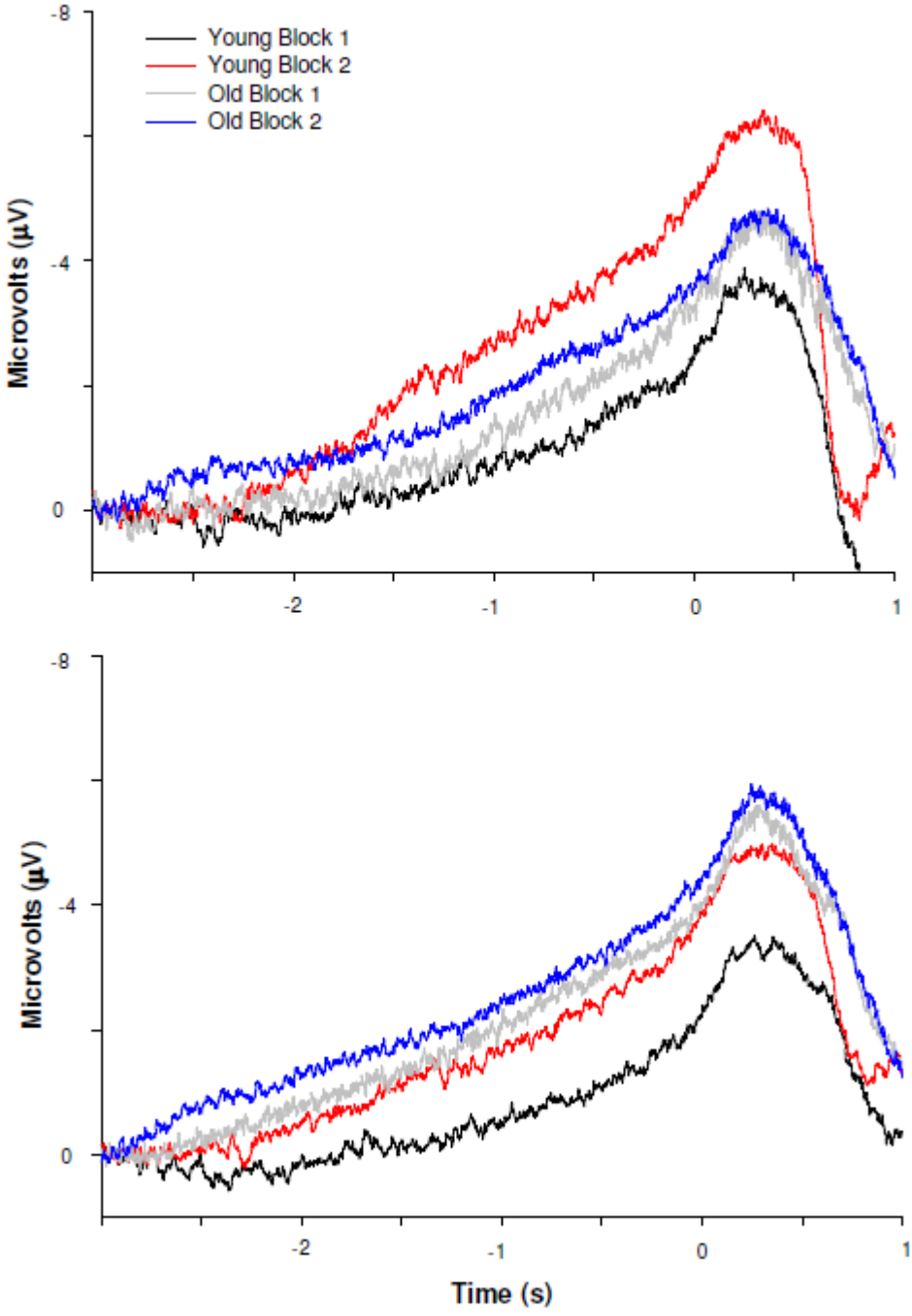
Young Block 1
Young Block 2
Old Block 1
Old Block 2
Microvolts (μV)
-8
-4
0
-2
-1
0
1
Microvolts (μV)
-8
-4
0
-2
-1
0
1
Time (s)

**Figure 11:**

2D topographical maps of component amplitudes. Note each map is oriented such that the anterior-posterior axis is arranged vertically with nasion located at the top.

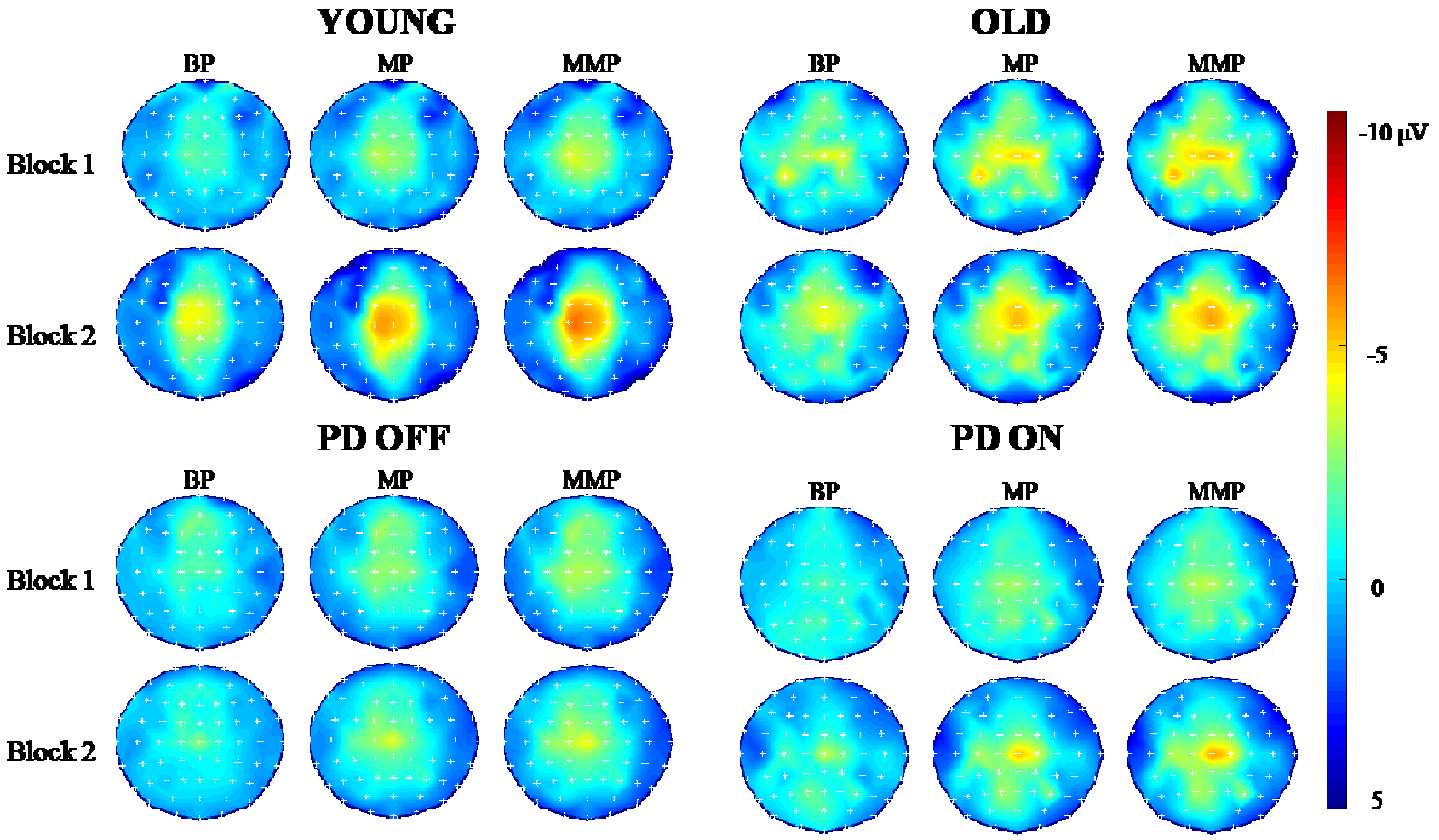
YOUNG
OLD
PD OFF
PD ON
BP
MP
MMP
Block 1
Block 2
-10 µV
-5
0
5

**Figure 12:**

Grand average MRCP waveform at CM (top) and LM (bottom) electrode sites for experiment 2.

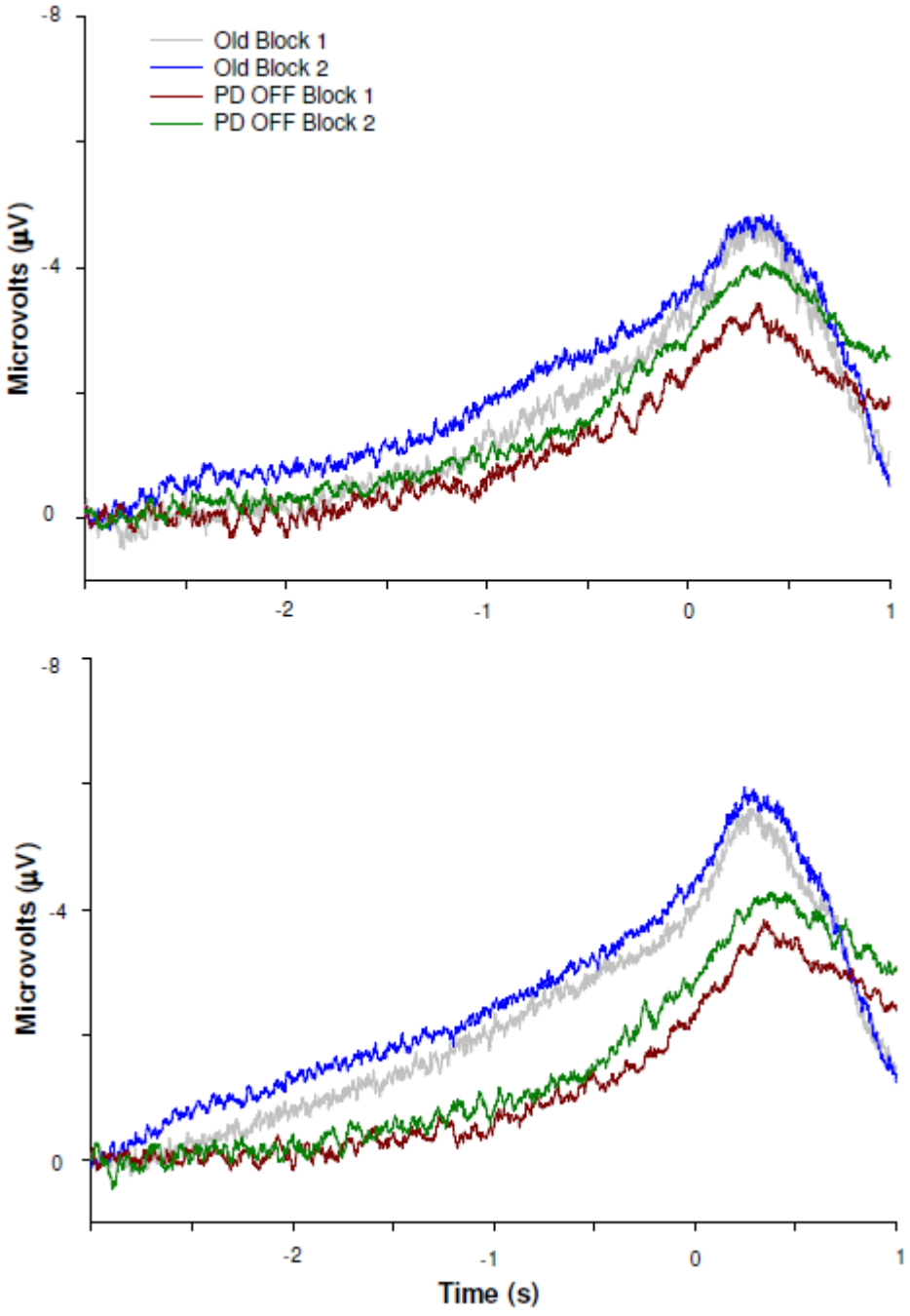
Old Block 1
Old Block 2
PD OFF Block 1
PD OFF Block 2
Microvolts (µV)
-8
-4
0
-2
-1
0
1
Microvolts (µV)
-8
-4
0
-2
-1
0
1
Time (s)

**Figure 13:**

Grand average MRCP waveform at CM (top) and LM (bottom) electrode sites for experiment 3.

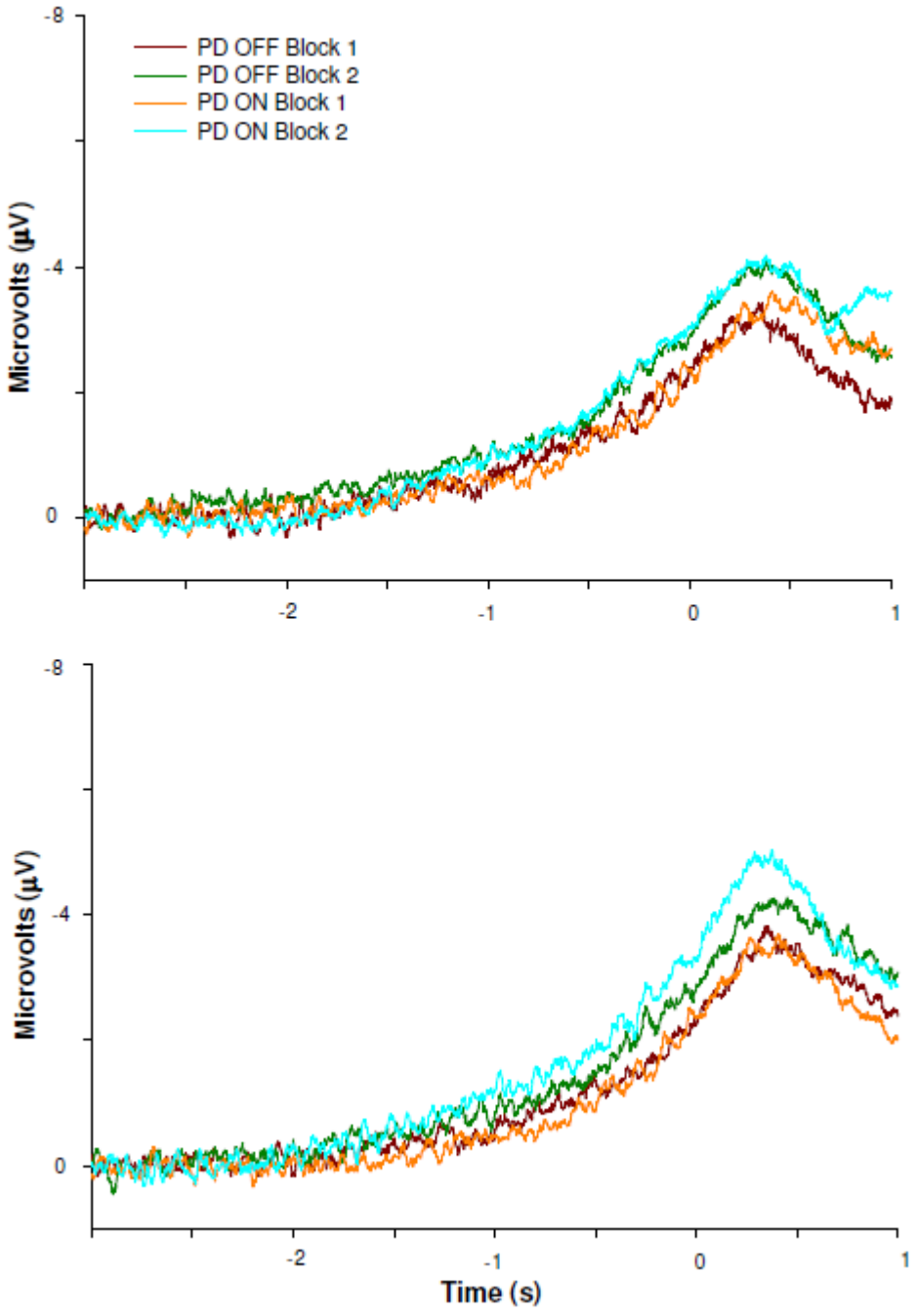
PD OFF Block 1
PD OFF Block 2
PD ON Block 1
PD ON Block 2
Microvolts (µV)
-8
-4
0
-2
-1
0
1
Microvolts (µV)
-8
-4
0
-2
-1
0
1
Time (s)

**Table 1:**

Clinical profile of 10 individuals with Parkinson disease

| Subject | Age (yrs) | PD Duration | UPDRS OFF | H&Y |
|---|---|---|---|---|
| **1** | 59 | 9 | 23 | 2 |
| **2** | 52 | 3.5 | 15.5 | 2 |
| **3** | 75 | 9 | 30.5 | 2 |
| **4** | 69 | 4 | 31 | 2 |
| **5** | 68 | 7 | 28.5 | 2 |
| **6** | 78 | 4 | 24 | 2 |
| **7** | 73 | 18 | 40.5 | 3 |
| **8** | 62 | 3 | 18.5 | 2 |
| **9** | 78 | 5 | 28 | 2 |
| **10** | 67 | 4 | 43 | 2 |

**Table 2:**

Maximal grip strength (kg).

| Subject | Young | Older | PD OFF | PD ON |
|---|---|---|---|---|
| **1** | 72.7 | 41.1 | 45.0 | 51.0 |
| **2** | 33.3 | 52.0 | 68.9 | 80.1 |
| **3** | 18.6 | 44.1 | 40.6 | 31.3 |
| **4** | 67.6 | 45.2 | 40.5 | 28.0 |
| **5** | 57.1 | 36.9 | 28.4 | 38.9 |
| **6** | 81.8 | 74.1 | 18.1 | 19.9 |
| **7** | 32.3 | 19.3 | 29.2 | 29.7 |
| **8** | 25.8 | 23.5 | 29.2 | 16.7 |
| **9** | 64.8 | 20.5 | 28 | 35.4 |
| **10** | 59.2 | 41.3 | 43 | 21.8 |
| **Mean (SD)** | 51.3 (21.9) | 39.7 (16.5) | 32.3 (17.9) | 35.3 (18.6) |

## Chapter 4: Conclusion

### *Summary of Findings*

Boyd et al. (14) recently summarized data demonstrating the potential for electrophysiology to inform clinical practice and serve as a supplement to assist in program design and evaluation. Further, they highlighted that this technology, which has only recently been visible in rehabilitation science, may be used clinically to detect neuroplastic change and recovery. Our work in *Chapter 2* is the first to utilize electrophysiological evidence in such a manner by reporting alterations in cortical activity in response to short-term lower extremity resistance training. We interpret our findings similarly to Carroll and colleagues (21) suggesting that a reduction in cortical activation is beneficial in reducing activation of neural elements unrelated to the intended movement, thereby resulting in enhanced efficiency.

Reducing the activation of neural elements unrelated to the desired movement is advantageous in terms of neural efficiency. However, this ability appears limited in older adults as previous studies have shown unique task-related activation whereby they recruit a much larger network than younger adults (16). This diffuse activity represents compensatory adaptation, but also illustrates an inability to selectively activate a given cortical network (76). The focus of *Chapter 3* was to extend these findings to a model that allowed us to study activation over the duration of a protocol rather than during isolated movements which have been documented previously. We found that young adults responded to central demands by augmenting activity within focal regions to maintain task performance. Further, this was achieved in the absence of peripheral changes (e.g. EMG, MVC), thereby demonstrating a prominent adaptation of the cortex

during repetitive grasping. However, we observed only minimal increases in these regions for older adults with or without PD. In addition, we found a slight improvement when individuals with PD performed the protocol while optimally medicated. Our results support the idea that age-related and neurodegenerative changes of the central nervous system alter the manner in which cortical activity responds to imposed demands.

### *Limitations*

Our electrophysiological approach has the advantages of excellent temporal resolution and can provide a direct measure to assess changes at the level of the cortex without the confounds of introducing artificial input (e.g. TMS) into the system (166). However, it suffers from poor depth resolution and limits our understanding of the involvement of subcortical structures.

One potential methodological limitation that is shared across studies is the limited EMG recording. For *Chapter 2*, recording of additional musculature of the lower extremity may have permitted us to better delineate the relative peripheral and central adaptations that occurred as a result of resistance training. In *Chapter 3*, we acknowledge our limited EMG recording does not adequately quantify peripheral adaptations (i.e. agonist/antagonist activation, synergist activation) that may have occurred over the duration of the 150 handgrip contractions. Although our study aims were centered upon supraspinal changes, the addition of multiple EMG locations may have provided useful information. However, due to our high-density EEG recording montage we had limited bipolar channels available for recording additional EMG, and our only alternative would

have been to omit EEG channels. Additionally, in order to accurately synchronize EEG, EMG, and force signals we used a single amplifier system.

A major disadvantage to EEG is its poor spatial-depth resolution. Several recent studies have identified disparate effects for cortical and subcortical structures in healthy aging and PD (72, 108, 111). Remedying this approach may include combining EEG with other neuroimaging and neurophysiological technologies. This has been shown to be quite advantageous in defining principal generator sources for components of the MRCP (98), and presumably would enhance the approaches taken in *Chapters 2 – 3*. The combination of EEG with neuroimaging techniques such as fMRI has seen great interest and new hardware and software developments have enabled their simultaneous recording (116). Along these same lines, the combination of EEG with the popular TMS technique is currently being investigated (10, 101). Miniussi and Thut (101) recently proposed that co-registration of EEG and TMS may offer the ability to better understand the activation sequence of various cortical areas due to their excellent temporal resolution and timing, respectively. The combination of brain stimulation or brain imaging with concurrent electrophysiological recording could dramatically enhance information obtained as compared to use of each method independently.

### *Clinical Implications and Suggestions for Future Studies*

Understanding the plasticity of the nervous system is essential in advancing rehabilitation research and may be decomposed into two main pursuits; 1) identifying the intervention and dose necessary for adaptation, and 2) associating that adaptation with a

functional outcome (133). These pursuits are made possible through neurophysiological techniques (i.e. EEG, fMRI, PET, TMS) that offer *in vivo* examination of brain plasticity.

In *Chapter 2*, we examined the cumulative effects of a resistance training intervention as our understanding of the mechanisms driving these adaptations is not well developed. We provide evidence that a dose of nine resistance training sessions induced adaptive alterations at the level of the cortex in young healthy adults. We interpret these adaptive changes in terms of neural efficiency which would be of particular utility to older adults who demonstrate over-activation of cortical motor regions (67, 100, 107, 156), as well as an inability to selectively activate cortical motor regions responsible for movement (76). Presumably, resistance training may be effective in this population for reducing cortical demands related to performance of motor tasks and improving efficiency. Although these studies have not yet been performed, we encourage research in this area to identify the optimal dose of activity as well as associating the response to activity with a functional outcome, such as sit-to-stand or six-minute walk performance.

The opportunity for future research targeted at the aforementioned pursuits of rehabilitation research (133) is considerable. However, intervention studies require careful design and consideration in order to best utilize resources and produce the greatest results, particularly when investigating clinical populations. For example, in individuals with PD there are noted deficits in SMA activation that have been associated with bradykinesia and reduced reaction times (29, 31). These cross-sectional investigations thereby provide a rationale for future interventions with the goal of enhancing SMA activation concomitant with improving clinical parameters of bradykinesia. Similarly, in *Chapter 3* we explored how central adaptive processes vary

as a function of aging, PD, and PD medication irrespective of baseline categorical differences. This approach was important for extending findings of previous studies that examined only 'simple' motor tasks in that we employed a more practical paradigm (e.g. repetitive grasping) that may be utilized in motor training. Therefore, our paradigm allowed us to monitor the central adaptive processes that take place during performance of a practical training session with respect to age, PD, and PD medication. This information would be particularly useful in the design of future rehabilitation trials that avoid applying a "one size fits all" approach. Future research may consider additional motor training paradigms as well as unique populations in a similar manner to that performed in *Chapter 3*. The ability to characterize adaptive responses as a result of exercise therapy will not only validate exercise prescription in health and disease, but provide the evidence necessary to provide the best care. The MRCP paradigm employed in *Chapters 2 -3* may be an appropriate tool to index these changes.

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